LONG-LASTING EFFECTS OF mTBI ON OCULOMOTOR ABILITY AND NEUROMUSCULAR CONTROL

by

Gustavo Sandri Heidner

July 2022

Director of Dissertation: Nicholas P. Murray

Department of Kinesiology

Concussions result in short-lived to long-lasting neurological function impairment and disturbances, typically undetectable by standard neuroimaging protocols, which can persist for several months post-trauma. Eye-tracking and virtual reality can be a powerful tool in the assessment of short- and long-term concussed individuals. However, it needs a clear and concise methodology. When acting as an optical flow-induced perturbation of balance metrics and combined with electroencephalographic data, it can differentiate between a non-concussed fatigue state and a concussive state. Furthermore, when employed as a secondary cognitive task, it elicits neural modulations and postural control perturbations that can detect concussion-related impairments up to eight years post-trauma. In this dissertation we sought to (i) develop a virtual reality environment that implements known eye-tracking methodologies and validate its accuracy in differentiating between non-concussed and concussed cohorts, (ii) investigate the presence of neural signatures that could differentiate between a concussive state and a fatigue state, and (iii) determine if long-lasting oculomotor and peripheral muscle control impairments could be reliably detected in a concussed cohort several years post-trauma. Our overarching hypotheses were that (i) eye-tracking metrics observed in a virtual reality environment can differentiate between non-

concussed and concussed cohorts, (ii) spectral power of cortical activations are different between non-concussed participants in a fatigued state and concussed participants, and (iii) oculomotor impairments and corticomuscular correlates of balance metrics can be detected in a concussed several months post-trauma. Our findings support the majority of the initial proposed investigation. We detected corticomuscular coherence and postural control differences capable of differentiating between non-concussed and long-term concussed participants, established a link between corticomuscular coherence and postural control adaptations observed in the concussed group, determined some limitations of virtual reality paradigms in concussion assessment.

Long-lasting Effects of mTBI on Oculomotor Ability and Neuromuscular Control

A Dissertation

Presented to the Faculty of the Department of Kinesiology

East Carolina University

In Partial Fulfillment of the Requirements for the Degree

Doctor of Philosophy in Bioenergetics and Exercise Science

By

Gustavo Sandri Heidner

July 2022

LONG-LASTING EFFECTS OF mTBI ON OCULOMOTOR ABILITY AND NEUROMUSCULAR CONTROL

by

Gustavo Sandri Heidner

APPROVED BY:

DIRECTOR OF DISSERTATION: ______________________________

Nicholas P. Murray, PhD

COMMITTEE MEMBER: ______________________________

Zachary J. Domire, PhD

COMMITTEE MEMBER: ______________________________

John Christopher Mizelle, PhD

COMMITTEE MEMBER: ______________________________

Stacey A. Meardon, PhD

COMMITTEE MEMBER: ______________________________

Bryan Sylcott, PhD

CHAIR OF THE DEPARTMENT OF

KINESIOLOGY: ______________________________

Joonkoo Yun, PhD

INTERIM DEAN OF THE GRADUATE SCHOOL: ______________________________

Kathleen T. Cox, PhD

DEDICATION

To my family, friends, and mentors who,

each in their own way,

contributed to this moment,

and to what I have become.

ACKNOWLEDGEMENTS

This dissertation would not be possible without the guidance from mentors, the help from colleagues, and the funding from the Office of Naval Research, the International Society of Biomechanics, and the Department of Kinesiology at East Carolina University.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS OR ABBREVIATIONS

Chapter 1: Review of Literature

Traumatic Brain Injuries

Traumatic brain injuries are a major health concern in the US. They have accounted for approximately 11% of the injury-related emergency department visits in 2013[1]. In the year 2000, the CDC estimated that 1.7 million people sustained a TBI in the US, with total costs of emergency department visits and hospitalization of approximately US$60 billion[2]. Fourteen years later, the CDC reported an approximately 70% increase in cases of TBI. There were a total of 2.87 million TBI-related emergency room visits, hospitalizations, and deaths in the US in 2014[1]. In 2017, there were approximately 224,000 hospitalizations and 61,000 deaths due to TBI. Out of all cases of TBI, as many as 75% are mild traumatic brain injuries or mTBI. To illustrate their relevance, a search on PubMed for the word "mTBI mild traumatic brain injury" returns over 4700 results, just in the past five years.

We present background information on mild traumatic brain injuries, delineating symptoms, prevalence, medical and financial significance, and current methods of diagnosis. Next, we introduce electroencephalography and corticomuscular coherence as means for concussion impairment assessment and present some data pertinent to our investigation.

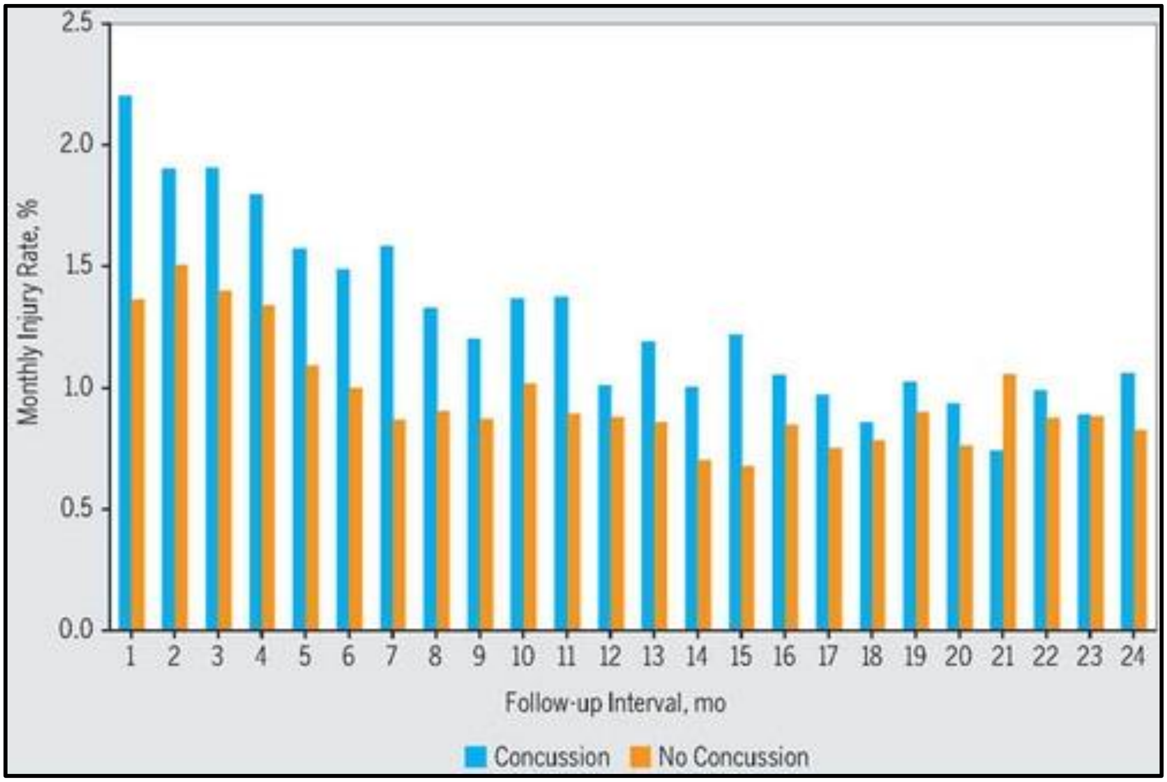
Concussion: Mild Traumatic Brain Injuries

Concussions or mTBI, a type of traumatic brain injury, are caused when an impulsive force is transmitted to the head, resulting in short-lived to long-lasting neurological function impairment[3]. The acute symptoms usually present themselves as a neurophysiological disturbance, undetectable by standard neuroimaging protocols[3]. Clinical symptoms may deteriorate into inflammation, cytoskeletal damage, and cell death, resulting in permanent neural damage[4]. The symptoms most commonly observed are a loss of concentration, anxiety, depression, fatigue, memory loss, visual defects, hearing defects, dizziness, and diplopia (double vision)[5]. These maladies present themselves immediately after a force is delivered to the head, evolving over the next minutes or hours[3,4], and can sometimes be detected or felt even one year posttrauma[5].

Given the severity and the prevalence of mTBI symptoms, several efforts have been made to quantify the incidence and to improve diagnostic methods. The military has reported an increase of 640% in the number of mTBI cases treated at DVBIC sites between 2005 and 2007[6]. However, the measurements of mTBI are yet largely inconclusive and not always accurate[7,8]. The Glasgow Coma Scale (GCS), commonly used to assess and classify TBIs, fails at the lower end of the spectrum when brain injuries are mild[7,9]. Other forms of assessment include measurements of level of TBI, a ranking of the person's level of consciousness, memory loss, and GCS score; speech and language skills tests; cognition and neuropsychological assessments[10]; and imaging tests, such as computerized tomography, magnetic resonance imaging, and intracranial pressure monitoring. Along with neuropsychological assessment and brain imaging methodologies, the balance impairment metrics to assess mTBI are only reliable during the first 1-2 weeks post-trauma, as the majority of these tested symptoms tend to disappear in early recovery[5]. However, some patients will have long-lasting effects of mTBI, also known as post-concussion syndrome, that may not be readily identified to be associated with it[11]. When post-concussion syndrome is thought to be present, the most common mechanisms of assessment are the ones developed by the *International Classification of Diseases(ICD-10)*[12] and the *Statistical Manual of Mental Disorder (DSM-V)*[13], but these mechanisms are indirect methods of evaluation, which are not accurate in detecting underlying motor control issues. Since posttraumatic mTBI effects do not yet have specific neuromuscular markers, the ability and the reliability of diagnostics is compromised. To accurately assess the health costs of mTBI, both personal and financial, it is imperative to discover and discretely define potential biological markers associated with it.

Earlier seminal data indicates that some patients can have long-lasting symptoms that can endure for over a year[5]. However, in most cases, recovery usually occurs within a couple of weeks post-trauma[2,3], and mTBI and post-concussive syndrome studies usually only investigate patients that are either still suffering the side-effects or presenting symptoms of mTBI, the data available have remained scarce when considering long-term motor control deficits that are not easily diagnosed. Despite what is known about the long-term issues by individuals that have sustained an mTBI, recent data suggests that the complications go beyond the lingering neurological and psychological conditions. A cohort study with 23,044 individuals points to a 38% increase, on average, in lower extremity injuries in soldiers that had sustained a concussion up to 2 years earlier in their lifetime, suggesting a higher risk of lower extremity musculoskeletal injury in physically active asymptomatic adults following concussion[14]. Within the first 15 months of sustaining a concussion, these individuals showed a 45% risk of injury, somewhat diminished during the following months 16-24 (Figure 1.1). This study provides some knowledge on the motor outcomes of mTBI, but it does not provide any data on neurological changes. Given that mTBI occurs due to trauma to the brain, non-invasive methods, such as electroencephalography, have also been shown to be a powerful tool in the study of this condition.

Figure 1.1. *Monthly lower extremity injury rate in physically active adults during 24 months after concussion (blue) compared to non-concussed (orange).*



Note. From Kardouni et al., 2018.

Electroencephalography

Electroencephalography is typically non-invasive electrophysiological method to record brain activity, in which electrodes are placed on the surface of the scalp. Commonly used in a 32, 64 or 128 channels configuration, it measures the spatial-temporal summation of electric potentials fluctuations within the skull[15], which are generated the axon membrane depolarization and repolarization. The method is not without limitations, as the EEG cap lies on the surface of the scalp, and the signal that it acquires is filtered through the skull, reducing its amplitude. Furthermore, the spatial resolution is not optimal, especially when trying to locate sources deeper within the brain. This limitation is known as volume conduction and is usually ablated by using several mathematical methods to refine source localization by removing cross-correlation between pools of neurons[16]. Given their location in the cortex, the majority of the EEG signal is obtained from the synchronous excitation and inhibition of pyramidal cells, but it has been shown that Glial cells also contribute to it due to their morphology and arrangement[15]. This is particularly interesting, as changes in Glial cell function were observed in animal models after mTBI[17,18].

The EEG signal can be analyzed in different manners. Frequency-domain, or power-based analyses, target certain frequency bands (i.e., delta = .5-4 Hz; theta = 4-8 Hz; alpha = 8-13 Hz; beta 13-30 Hz; gamma = 30+ Hz) that can be associated with activity in certain areas of the brain. This type of analysis describes the magnitude of brain activity within the EEG frequency bands[19]. Temporal correlation or coherence-based analyses are performed to investigate connectivity between areas of the brain. Time-domain analyses are usually performed in combination with specific events, for the study of ERPs, or by searching for specific waveforms that repeat over continuous EEG signal[20]. A higher signal correlation is found for time series that co-vary together[21], and this is believed to be evidence of neural communication. There are several studies about mTBI that have been published using these types of analyses.

There seems to be no consensus on the results derived from power analyses. The works of peers further illustrate some of the inconsistencies in results. Thompson *et al.* (2005) reported a decrease in alpha, beta, and theta power spectra in concussed athletes when compared to healthy controls[22]. Unrelated to the previous example, Munia *et al.* (2016) found evidence of altered delta and gamma activity as long as 10 and 12 months after subjects had sustained a concussion[23]. Teel *et al.* (2014) investigated connectivity and reported that although there was a decrease in alpha, beta, and theta power across the scalp, there was increased coherence in each band when compared to controls[24]. Two of those studies also reported conflicting data on brain connectivity. Cao & Slobounov (2010) indicated a significant decrease in the long-distance connectivity and a significant increase in the short-distance connectivity in mTBI patients when compared to controls[25], while Virji-Babul *et al.* (2014) reported differences in the local, but not global network[26]. The biggest limitation of most of these studies is that they lack a pre-concussion baseline and, therefore, rely solely on the comparison between concussed subjects and non-concussed healthy controls.

Other studies of clinical samples have also alluded to the usefulness of EEG as a method of identifying functional electrophysiological changes that may occur to the cerebral cortex post-mTBI[27–29]. Kaltiainen *et al*. (2018) found significantly increased theta-band oscillations in patients 6 days to 6 months post-concussion, even when structural lesions were not present in MRI[28]. Lewine *et al.* (2019) compared cortical activity of healthy and mTBI patients, and found global relative increased theta power, decreased global relative alpha power, and global beta-band interhemispheric coherence in mTBI patients[29].

Motivation

New technology has the potential to broaden the assessment efforts and may help alleviate the challenges in detecting long-term impairments post-concussion[30]. Of particular interest for us, in this study, is the combination of virtual reality and eye tracking technology, which was not available until recent years. Eye tracking studies are typically conducted in laboratorial settings, with the stimulus displayed on a monitor and the participant in a static position, often sitting down, in front of a computer screen[31]. These simulations are often not as immersive as real-world tasks, e.g., tacking a baseball moving towards you in 3D space. It is also possible that depth perception is altered due to the locational cues in the environment around the patient. More specifically, the patient observes the paradigm on a screen, but the screen has a fixed distance from the eyes, and the environment around it has varying depths, e.g., chairs, tables, walls, and ceiling.

Virtual reality environments can overcome the space and depth confounding variables by placing the participant in a completely immersive optical flow paradigm without outer distractions[32]. Moreover, the configuration of the eye trackers inside VR googles make them always optimally placed in relation to the patient's eyes, therefore eliminating potential issues due to minor head and trunk movements. With that in mind, myriad scientific questions likely need to be asked before further inference can be made on the efficacy of using VR-embedded eye tracking systems to assess concussion impairments. One such questions is the reproducibility of protocols.

Eye tracking protocols can vary substantially between research settings. However, there are some methodologies that are widely accepted by researchers in the field, such as paradigms that elicit slow and ballistic eye movements. In virtual reality, the possibility of variance in protocols is exponentiated due to the limitless creative capacity afforded by it. Therefore, we have established that the first aim of this investigation would be to (i) implement a standard, static, eye tracking paradigm in a virtual reality environment that offers immersion and depth perception, as well as being standardized for all participants, and (ii) determine if this implementation could detect differences between concussed and non-concussed participants.

Another concern of ours was to understand if our test results could be influenced by extraneous factors. For example, it is not uncommon for athletes and warfighters to sustain a concussion while performing exerting physical activity[33], and it is yet unclear if the momentary effects of this physical exertion can obscure the results of concussion testing using virtual reality-induced optical flow perturbations[34]. Thus, our second aim was to investigate the effects of a somewhat hard-to-hard physically exerting protocol in the electroencephalographic profile between concussed and non-concussed participants during a series of balance perturbation tasks. More specifically, to determine if there were brain activity markers that could differentiate between to disparaging groups.

The balance perturbation tasks introduce a dynamic task component dependent on postural control in recently concussed participants. It is not guaranteed that the differences observed would be detectable for longer periods of time after assumed recovery. Therefore, our third aim was to investigate the long-lasting impairment effects of concussion on oculomotor function, atypical postural control, and the corticomuscular coherence of lower extremity muscles in a young adult collegiate cohort. Our objectives were to verify (i) if the impairments were detectable with eye tracking, electroencephalography, and balance metrics while being perturbated by a dynamic optical flow task in virtual reality.

The sum of specific aims in this study were:

- Aim 1: Develop a virtual reality environment that implements known eye-tracking methodologies and validate its accuracy in differentiating between non-concussed and concussed cohorts.
    - Overarching hypothesis: Eye-tracking metrics observed in a virtual reality environment can differentiate between non-concussed and concussed cohorts.
- Aim 2: Investigate the presence of neural signatures that could differentiate between a concussive state and a fatigue state.
    - Overarching hypothesis: Spectral power of cortical activations are different between non-concussed participants in a fatigued state and concussed participants.

- Aim 3: Investigate the long-lasting oculomotor impairments and corticomuscular correlates in a concussed cohort several years post-trauma by using a combination of virtual reality paradigms and balance testing.
    - Overarching hypothesis: Impaired oculomotor function are detectable several years post-trauma and balance deficits are related to changes in neural modulations observed in the frontal and sensorimotor cortexes.

Chapter 2: Virtual Reality Eye-Tracking Methods: Concussion Screening

Abstract

Oculomotor control may be impaired by concussions due to their reliance on coordination and timing of the neural pathways between areas of the brain. Impairments observed in saccadic eye movements have been linked to suboptimal brain function. Eye-tracking in a virtual reality environment can provide an immersive and controlled testing environment. A cohort of 29 concussed and 53 non-concussed participants performed common eye-tracking paradigms while in a virtual reality environment: circular smooth pursuit, vertical/horizontal smooth pursuit, and vertical/horizontal saccades. The combined results for circular smooth pursuit, horizontal smooth pursuit, vertical smooth pursuit, horizontal saccades, and vertical saccades suggests that concussed participants can be differentiated from non-concussed controls in terms of error, standard deviation of error, root mean square of error, and angular error. Some eye-tracking paradigms may be more effective at differentiating between concussed and non-concussed cohorts. Precisely, in this protocol, horizontal saccades were effective while horizontal smooth pursuits, vertical smooth pursuits, and vertical saccades were not.

Introduction

The investigation of abnormalities in eye movements after brain injury is interesting because of their reliance on coordination and timing of the neural pathways between the frontal lobe, basal ganglia, superior colliculus, and the cerebellum[35]. Impaired saccadic movements have been shown to indicate suboptimal brain function beyond the influence of depression, malingering, and intellectual ability in post-concussion syndrome subjects[36]. Saccades are fast eye movements that attempt to maintain the stimulus on the fovea by predicting the stimulus' position, velocity, and acceleration, while smooth pursuit are slow voluntary eye movements (~100 ms latency) with the objective of keeping the stimulus, typically a slow-moving target, on the fovea[37,38]. Smooth pursuit can occur in a linear[39] or circular fashion, or a combination of both[40]. When compared to non-concussed controls, mTBI patients have higher initial and final position error, as well as lower predicted velocity and acceleration, with increased predicted duration of saccadic movements when performing an horizontal displacement task[35]. The analysis of saccadic and smooth pursuit movements may be an important tool in the diagnosis of acute mTBI and post-concussive syndrome, as poorer saccadic movements may indicate injury in key cortical areas. Saccadic movements are also important correlates of cognitive processes during visual searches[41] and of attentional focus during tasks in which superior target detection and identification are required[42]. Therefore, impairments in saccadic eye movements due to mTBI have the potential to hinder individuals across all activities that require visual sensory input. In recent years, with the advent of eye-tracking technology in virtual reality (VR) settings, different eye-tracking methodologies became possible.

Virtual reality provides myriad advantages to challenge the oculomotor system. Virtual reality goggles prevent distractions from occurring due to extraneous visual stimuli. Likewise, VR goggles maintain a standard distance between the eyes and tracking cameras for all participants. With environments completely developed in game engines, e.g., Unity, VR also affords complete stimulus control and allows for standard and reproducible environmental protocols. Also, stereoscopic displays inside the goggles allow the perception of motion-in-depth stimuli. Finally, VR environment can be modified in real-time and respond to the participant's status. A few studies have recently employed VR as a method to deliver oculomotor paradigms that challenge the visual and vestibular system with the purpose of identifying markers of long-lasting effects of mTBI[43] or to assess residual executive disfunction[44] and balance impairments post mTBI in military personnel[45].

As such, the combination of eye-tracking and virtual reality can potentially be a powerful research and diagnostics tool for both short- and long-term mTBI patients. However, before it can be used effectively as a clinical tool, we must understand how it works and how it performs in a laboratory setting. Environments developed for VR applications have an infinite number of ways in which they can designed. Therefore, eye-tracking paradigms delivered in VR environments require a clear methodology. Moreover, being a relatively new technology means that there is no software for direct and straightforward data processing. In this report we provide a well-defined virtual environment, with integrated saccadic and smooth pursuit functionalities. Likewise, we describe the data processing and results for a sample of young adults with or without mTBI, and how this method can distinguish between two disparate groups. Our specific aim was to develop a virtual reality environment that implements known eye-tracking methodologies and validate its accuracy in differentiating between non-concussed and concussed cohorts. Our hypothesis was that eye-tracking metrics observed in a virtual reality environment can differentiate between non-concussed and concussed cohorts.

Methods

Participants

A total of 92, healthy and clinically diagnosed concussed participants aged 18-35 years with normal or corrected-to-normal vision (i.e., contact lenses) were enrolled in this research. Self-reported diagnosis from a clinical practitioner (e.g., physician, physical therapist, athletic trainer) was required to be included in the concussed group. Participants that did not meet the inclusion criteria were excluded. Subjects were also excluded if they had been previously diagnosed with any of the following conditions: (i) ocular, auricular, or neurological abnormalities that impact visual and hearing function, or (ii) history of stroke or neurodegenerative disease.

Virtual Reality Environment Eye Tracking

An HTC VIVE virtual reality headset with integrated Tobii Pro infrared eye-tracking system was used to track focal vision during VR simulations. The HTC Vive headset has a binocular screen configuration that delivers optical flow based on pre-built VR environments, with a refresh rate of 90 Hz at 4K resolution. The Tobii Pro eye-tracking system is composed of two infrared cameras, one for each eye, and two circular arrays of infrared light dots. The infrared light is reflected by the retina and captured by the cameras, providing positioning of the eyes.

Circular smooth pursuit (CSP), horizontal smooth pursuit (HSP), vertical smooth pursuit (VSP), horizontal saccades (HSA), and vertical saccades (VSA) paradigms were developed in Unity. The participant was placed within four walls with an open skybox. Walls were high enough that when looking ahead, the participant could not see above them. The open ceiling (skybox) design was chosen to introduce realistic parameters into the scene, such as dynamic shadows. The floor was tiled with a texture that resembled stone squares. The walls were painted with a dark green and checkered pattern to aid with depth perception. A 3D ball-shaped object was used as visual focus. This target was a purple ball of 0.52° diameter of visual angle.

Eye tracking and VR headset position data from Unity are saved in an Extensible Markup Language (XML) file. This file format is similar to HTML but affords the programmer the ability to create their own tags for each data type. In the example below, we can see the structure of each data point saved in XML format. The first attribute of the data point is a time stamp (GazeData TimeStamp) in microseconds, measured from an arbitrary point in time. Next, we have the tag "ObjectCoordinates," which holds the cue position in 3D virtual space. All measurements in VR space are relative to a chosen reference and measurement system. By default, unity uses increments of 1 arbitrary unit, which are commonly treated, or defined, as being one meter (1 m). The values in parenthesis follow the convention of Cartesian systems *(x, y, z)*, with the default axes orientations in Unity being lateral (*x*), vertical (*y*), and longitudinal (*z*); positive to the right/up/forward. In this example, the cue is located 1.299m to the right, 1.771m up, and 6m away from the origin. In the second line, we have "Pose Position" and "Rotation," two variables relative to the location of the eyes in the headset. Pose position is also a 3D Cartesian coordinate, with the same configurations as the cue coordinates. Rotation is represented as a quaternion of terms (*x, y, z, w*), in which *w* corresponds to the angle of rotation and the vector term (*x, y, z*) indicates the axis of rotation.

The data points described so far define the VR environment in space-time, place the cue inside the environment, and define the position and rotation of the eyes in relation to the origin. Next, we have the three main data structures for eye tracking: "Left" (left eye), "Right" (right eye), and "CombinedGazeRayWorld" (stereoscopic gaze). Both left and right eye have the same tags. Gaze direction is a 3D unit vector. Gaze origin is the (*x, y, z*) relative position of gaze origination for that specific eye. Pupil diameter is in meters. Finally, "GazeRayWorld" is the calculated gaze for each individual eye, with an "Origin" position relative to the environment's origin, and a "Direction" 3D unit vector. "CombinedGazeRayWorld" is the gaze resultant from the combination of data from both eyes, with an "Origin" position relative to the VR environment's origin, and a "Direction" 3D unit vector. The "Valid" tag in each field is a confirmation that the data point is valid, i.e., there were no issues with its acquisition and/or recording. A value of “False” would indicate a data point that must be discarded.


```
<GazeData TimeStamp="1599359856" ObjectCoordinates="(1.299, 1.771, 6)">
  <Pose Position="(-0.309, 1.804, -0.361)" Rotation="(-0.077, 0.016, -0.007, 0.996)" Valid="True" />
  <Left>
    <GazeDirection Value="(0.089, -0.220, 0.971)" Valid="True" />
    <GazeOrigin Value="(-0.0308, 0.002, -0.0163)" Valid="True" />
    <PupilDiameter Value="0.00328996" Valid="True" />
    <GazeRayWorld Origin="(-0.340, 1.804, -0.376)" Direction="(0.119, -0.069, 0.990)" Valid="True" />
  </Left>
  <Right>
    <GazeDirection Value="(0.061, -0.314, 0.947)" Valid="True" />
    <GazeOrigin Value="(0.0321, 0.002, -0.0172)" Valid="True" />
    <PupilDiameter Value="0.00266736" Valid="True" />
    <GazeRayWorld Origin="(-0.277, 1.803, -0.380)" Direction="(0.089, -0.1647, 0.982)" Valid="True" />
  </Right>
  <CombinedGazeRayWorld Origin="(-0.308, 1.804, -0.378)" Direction="(0.104, -0.117, 0.987)" Valid="True" />
```


Experimental Protocol

Participants gave informed consent upon arrival to the lab. They were asked to complete a survey addressing their concussion history. Participants were then seated comfortably on a chair and asked to complete the five vision tasks (conditions) in the VR environment: CSP, HSP, VSP, HSA, and VSA. Each task consisted of three trials with a duration of 30 seconds each. The order of conditions was randomized and counterbalanced. Participants were given a brief period of rest between trials and were instructed to request larger rest if they felt fatigued. The eye tracker was calibrated (5-point calibration) before the beginning of each session and whenever the goggles needed to be readjusted/were moved. Eye tracking data were collected at a sampling frequency of 120 Hz.

Data Reduction

A Python script was used to extract the relevant data from the .XML files. The original sampling rate of 120 Hz was unchanged. The timestamp for each data point was converted to milliseconds by dividing the value by 1000. Time zero (t0) was established as the first valid time point in milliseconds. Next, the script iterated over every data point checking that the data point was valid before extracting six variables: time range, left eye direction and origin, right eye direction and origin, and cue position.

Time range is the range of time since the beginning of the trial (t0) to the end of the trial (variable; at least 30 s). Time range was later used to extract an epoch of time starting five seconds after t0 and spanning for the next 20s. Left and right eye direction and origin were used to calculate left and right gaze x-y transform starting at the center of the pupil and extending for 6m to the x-y plane where the cue was located (Eq. 1).

Eq. 1: $$Gaze\ Point\ Transform\ = Direction_{Unit\ Vector} * \frac{6-Origin_{Position}}{|Direction_{Unit\ Vector}|}$$

This coordinate represents where the vector originating from each eye landed on the plane where the cue was presented, six meters away. Next, a constraint was applied to the gaze points to identify potential artifacts that needed to be filtered. Eye movements with an angular velocity greater than 900 deg. • s^{-1} were considered too fast to be natural biological responses. This was achieved by obtaining the squared root of the sum between two squared neighboring gaze points (x_i, y_i) and (x_f, y_f), divided by the range to the plane, and multiplied by the sampling frequency (Eq. 2).

Eq. 2: $$V_{angular} = \frac{\sqrt{(x_f - x_i)^2 + (y_f - y_i)^2}}{6} \text{ x } 120$$

Those data points were excluded from further calculations. At this point, data were reduced into 20-second epochs. Since we were interested in absolute error, and absolute error is either zero or positive, we opted to use a squared error formula to avoid negative values. Squared tracking error between the cue position and focal gaze position was then calculated for each eye across the whole epoch as the linear difference between the squared x-y position of the cue and the squared x-y position of the gaze point for the corresponding eye (Eq. 3).

Eq. 3: $$Squared\ Linear\ Error = (X_{Gaze} - X_{Cue})^2 + (Y_{Gaze} - Y_{Cue})^2$$

Similarly, angular error was calculated by taking the arc tangent of the root-mean-squared of the x-y position of the cue and the x-y position of the gaze point for each eye, adjusted for the distance from the plane (Eq. 4).

Eq. 4: $$Angular\ Error = \tan^{-1}\left(\frac{\sqrt{(X_{Gaze} - X_{Cue})^2 + (Y_{Gaze} - Y_{Cue})^2}}{6}\right)$$

Next, the root-mean-square of error across the whole epoch for each eye was calculated by taking the square root of the sum of all squared error points, divided by the number of data points (Eq. 5).

Eq. 5: $$RMS_{error} = \sqrt{\frac{\sum_1^N Squared\ Linear\ Error}{N}}$$

Finally, the mean and standard deviation of the squared error were calculated. Sample entropy was calculated as an additional measurement of variance (See Lake et al., 2002). The outcome variables of the data analysis process were the mean squared error of the left (E_L) and right eye (E_R), the standard deviation of mean squared error of the left (SD_L) and right (SD_R) eye, angular error of the left (A_L) and right (A_R) eye, sample entropy for the left (ENT_L) and right (ENT_R) eye, and the root-mean-square of error for the left ($RMSE_L$) and right (RMS_R) eye.

Statistical Analyses

Data were analyzed using IBM SPSS Statistics for Windows (Version 27.0. Armonk, NY: IBM Corp). Normality was assessed by dividing *Skewness* by the *S.E. of Skewness*, and *Kurtosis* by the *S.E. of Kurtosis*. A critical value of $z = .01$ was used to test this hypothesis. A two-way multivariate analysis of variance (MANOVA) was conducted to test the hypothesis that there would be one or more mean differences between groups (healthy, concussed) and conditions (CSP, HSP, VSP, HAS, VSA) based on the dependent variables (E_L, E_R, SD_L, SD_R, A_L, A_R, ENT_L, ENT_R, $RMSE_L$, RMS_R). Pairwise comparisons were performed with Bonferroni correction. The level of significance was set at $\alpha = .05$.

Results

All enrolled participants completed the protocol. After initial processing and inspection, data from four participants were excluded. The final sample consisted of 86 participants ($N = 86$; $n_{concussed} = 30$). None of the data were normally distributed. Box's test of equality of covariance matrices revealed that the assumption of homogeneity of variance-covariance matrices was violated, Box's M = 5835.94, F(495, 87722.58) = 10.48, p < .001.

A statistically significant effect was observed between groups, Wilk's Λ = .99, F(10, 396=5) = 2.57, p = .005. Levene's test for equality of variances was violated for all dependent variables, all p < .001. The test of between-subjects effects revealed a significant main effect of concussion in the squared error in the left eye (E_L), F(1, 404) = 4.50, p = .034, ηp^2 = .011, the standard deviation of error in the left eye (SD_L), F(1, 404) = 5.89, p = .016, ηp^2 = .014, the root-mean-square of error in the left eye ($RMSE_L$), F(1, 404) = 5.46, p = .020, ηp^2 = .013, and angular error of the left eye (A_L), F(1, 404) = 4.27, p = .039, ηp^2 = .010. Pairwise comparisons with Bonferroni correction revealed that concussed participants had increased SD_L, p = .016; $RMSE_L$, p = .020; E_L, p = .034; and A_L, p = .039.

Individual independent samples Student's t-tests were performed to investigate which specific conditions were responsible for discerning between concussed and healthy participants. When separated by conditions, all dependent variables met Levene's test for equality of variances, all p > 0.01. The results are summarized in Table 1.1.

Table 1.1. Summary of Statistics for Eye Tracking Metrics

		Healthy		Concussed					
		M	*SD*	*M*	*SD*	*df*	*t*	*p*	Cohen's *d*
CSP	E_L	.54	.43	.74	.64	80	-1.68	.097	.366
n_h = 53	SD_L	.26	.18	.36	.26	80	-1.85	.067	.447
n_c = 29	$RMSE_L$	.60	.46	.83	.68	80	-1.73	.086	.396
	A_L	.08	.06	.11	.10	80	-1.64	.145	
HSP	E_L	.27	.20	.30	.20	80	-.75	.452	
n_h = 53	SD_L	.17	.10	.20	.10	80	-.95	.341	

n_c = 29	RMSE$_L$	.32	.23	.37	.22	80	-.83	.408	
	A$_L$	.04	.03	.05	.03	80	-.76	.449	
HSA	E$_L$	1.01	.10	1.06	.18	83	-1.44	.152	
n_h = 56	SD$_L$	.88	.09	.92	.08	83	-2.03	.045*	.469
n_c = 29	RMSE$_L$	1.35	.09	1.41	.19	83	-1.78	.078	.403
	A$_L$	.16	.01	.17	.02	83	-1.39	.166	
VSP	E$_L$	.31	.21	.35	.31	83	-.55	.581	
n_h = 55	SD$_L$	.19	.12	.19	.26	83	-.07	.943	
n_c = 30	RMSE$_L$	.37	.25	.41	.39	83	-.55	.579	
	A$_L$	.05	.03	.05	.04	83	-.50	.614	
VSA	E$_L$	.40	.31	.43	.27	78	-.37	.722	
n_h = 54	SD$_L$	.51	.21	.56	.20	78	-1.04	.298	
n_c = 26	RMSE$_L$	.67	.36	.72	.31	78	-.65	.515	
	A$_L$	.06	.05	.07	.04	78	-.35	.724	

Note. *M* = mean; *SD* = standard deviation; *df* = degrees of freedom; E$_L$ = left eye; SD$_L$ = standard deviation of error in the left eye; RMSE$_L$ = root-mean-square of error in the left eye; A$_L$ = angular error of left eye; CSP = circular smooth pursuit; HSP = horizontal smooth pursuit; HSA = horizontal saccades; VSP = vertical smooth pursuit; VSA = vertical saccades; n_h = sample size of non-concussed group; n_c = sample size of concussed group.

Discussion

In this study we sought to describe the methodology surrounding the combination between eye-tracking and virtual reality as means of concussion testing. The virtual reality environment deployed had built-in eye-tracking paradigms that are commonly used to produce smooth pursuits and saccades. Furthermore, we sought to demonstrate how this methodology can be used to distinguish between previously concussed and non-concussed cohorts. Overall, we have found that conventional eye-tracking tasks implemented in a VR environment can differentiate between two disparate groups. The combined data of circular smooth pursuit, horizontal smooth pursuit, vertical smooth pursuit, horizontal saccades, and vertical saccades suggests that concussed participants can be differentiated from non-concussed controls in terms of error, standard deviation of error, root mean square of error, and angular error.

In the current context of concussion screening, assessment of oculomotor function stands as a valuable tool in the monitoring of post-concussive symptoms[47]. Analyses of saccadic and smooth pursuit eye movements are correlated to symptom severity[36] and may be associated with cumulative effects of repeated neurological damage[48]. Oculomotor testing is also becoming more common in sideline screening, as a guide for specialized referral and further assessment or treatment[49], even as an indicator of vestibular impairment post-concussion[50]. In most cases, there are evidence of disrupted tracking ability, conducive to an increase in linear and angular error during oculomotor task[47,51]. In the near future, we may see these assessments become more widespread during all stages post-concussion events, from initial diagnosis to long-term screening of recovery.

Interestingly, independently of the metric chosen for analysis, participants' left eye appeared to be the most impaired when executing these eye tracking paradigms in VR. This finding brings to the fore one of the limitations of this study, i.e., we did not account for eye dominance in the data, which may be a limiting factor[52]. However, assuming the prevalence of right eye dominance in the population, it is safe to expect poorer left eye motor control in a randomly sampled population. Independent evaluation of the efficacy of each eye-tracking paradigm revealed that some may be more effective at differentiating between concussed and non-concussed cohorts. To be precise, in this protocol, horizontal saccades were effective while horizontal smooth pursuits, vertical smooth pursuits, and vertical saccades were not. Circular smooth pursuits showed promising results but were nonetheless not statistically significant. These findings differ slightly from Heitger et al. (2009), however we should note that the saccadic and circular smooth pursuit protocols are substantially different between both studies.

Our protocol used a simplified approach that may not have introduced enough complexity to fully challenge the participants, although similar paradigms produce consistent results within the same metrics in studies done outside of a VR environment[31]. It is possible that the perception demands introduced with the 3D environment significantly affect the outcome measures[53]. Specifically, EEG analyses of the cognitive load during the observation of 2D mapping and 3D projection tasks indicate higher cognitive processing is required to interpret the 2D task[54]. The choice of Bonferroni corrections was also quite conservative. It is possible that more statistically significant changes were not observed in post-hoc univariate testing due to this choice. Nevertheless, the MANOVA results established that the independent grouping variables simultaneously explained the variances observed between groups. In other words, when analyzed individually, these metrics are not sufficient to assess long-term mTBI oculomotor impairments, but they are sufficiently sensitive for that purpose when analyzed together.

Lastly, the time since concussion ranged from two weeks to seven years and was not large enough to allow its division in more uniform groups according to time since concussion. This study is not without limitations but offers promising insights into future research endeavors depending on eye-tracking VR protocol development. We believe the next steps would be the investigation of how certain parameter variations, e.g., cue size and velocity, can affect the results. Not only that, but it may be beneficial to explore more complex tracking tasks that incorporate smooth pursuits and more variants of saccadic parameters, e.g., angular displacement and velocity.

Chapter 3: Concussed Neural Signature is Substantially Different Than Fatigue Neural Signature in Non-concussed Controls

Gustavo Sandri Heidner[1] (ORCiD: 0000-0003-4578-9212, Twitter: @thebiomechman), Caitlin O'Connell[1] (ORCiD: 0000-0002-6767-8807), Zachary J. Domire[1] (ORCiD: 0000-0003-4590-4583, Twitter: @ecu_pol), Patrick Rider[1], Chris Mizelle[1] (ORCiD: 0000-0002-5123-5673), Nicholas P. Murray[1] (ORCiD: 0000-0001-9968-2109, Twitter: @Visual_Motor)

[1]*Department of Kinesiology, East Carolina University, Greenville, NC, USA*

Corresponding Author:

Nicholas P. Murray, PhD

East Carolina University

College of Health and Human Performance

Department of Kinesiology

72 Minges, 100 Ficklen Dr.

Greenville, NC 27858

murrayni@ecu.edu

(252) 737-2977

Abstract

Traumatic brain injuries can result in short-lived and long-lasting neurological impairment. Identifying the correct recovery timeframe is challenging, as balance-based metrics may be negatively impacted if testing is performed soon after exercise. Thirty-two healthy controls and seventeen concussed individuals performed a series of balance challenges, including virtual reality optical flow perturbation. The control group completed a backpacking protocol to induce physical exertion. Concussed participants had lower spectral power in the motor cortex and central sulcus when compared to fatigued controls. Moreover, concussed participants experienced a decrease in overall theta band spectral power while fatigued controls showed an increase in theta band spectral power. This neural signature may be useful to distinguish between concussed and non-concussed fatigued participants in future assessments.

Keywords: concussion; fatigue; EEG; neural signature; virtual reality

Introduction

Traumatic brain injuries can result in short-lived and long-lasting neurological impairment and identifying the correct recovery timeframe is challenging. Fatigue induced by physical exertion can negatively impact balance-based metrics due to muscular fatigue[55] and increased use of cognitive resources for postural control[56]. This can be problematic when time is of the essence, i.e., in deployed service men and women. Another factor that must be taken into consideration is that some populations, with similar duties to warfighters, may not afford the chance to be tested immediately after injury or while completely at rest. More specifically, some patients may not have access to testing within the first two weeks. In cases in which they do have access to a deployable field test for mTBI, the protocol would need to account for confounding factors, such as the effects of physical and mental fatigue on balance.

Balance represents the final common output of a complex and dynamical system that is susceptible to challenges from many sources, including illness and injury, as well as sensory perturbations. There has been a marked increase in the commonality of balance testing for the assessment of concussive symptoms[47,51,57]. In some cases, although rare, balance testing may be available for immediate sideline testing[47], where confounding issues abound. Fatiguing activities create a mismatch between central nervous system control and mechanical output. Muscles have lower neural excitation and are less responsive to balance perturbations when fatigued[58]. This lower responsiveness causes modifications in motor control output, postural control, and increases the risk of injury[59]. Fatigue can be induced at the whole-body level or at local muscle level. Whole-body fatigue involves multi-joint muscle groups and has greater metabolic costs while local muscle fatigue only affects the neuromuscular system. Thus, whole-body physical fatigue deteriorates sensory integration of proprioceptive and exteroceptive feedback[60]. One of the unique strengths of using balance is its sensitivity to mechanical and optical-flow-induced perturbations, which provides the ideal environment to study the central neural origins of balance control using EEG assessments and virtual reality interventions.

Electroencephalography is a typically non-invasive electrophysiological method to record brain activity, in which electrodes are placed on the surface of the scalp to measure the spatial-temporal summation of electric potentials fluctuations within the skull[15]. A review study by Conley et al. (2019) focused on the resting-state EEG of athletes that had suffered an mTBI found sixteen studies that included 506 concussed athletes, with thirteen of those studies including 367 non-concussed healthy athletes as controls. Of the reviewed studies, ten of them drew comparisons between concussed and controls without a pre-concussion baseline, while four studies compared baseline and post-concussion with controls, and two only assessed athletes after concussion. Seven studies utilized a power-based approach in their analysis. Thompson reported a decrease in alpha (~8-12 Hz) and theta (~4-8 Hz) power spectra in concussed athletes when compared to healthy controls. Similarly, Teel et al. (2014) reported a decrease in alpha and theta power across the scalp and increased coherence in each band when compared to controls. Kaltiainen et al. (2018) found significantly increased theta-band oscillations in patients 6 days to 6 months post-concussion, even when structural lesions were not present in MRI. Lewine et al. (2019) compared cortical activity of healthy and mTBI patients and reported a global relative increase of theta power and decrease of alpha power in mTBI patients. It appears that mTBI generally leads to short and long-term loss of alpha and theta power all over the brain. In some cases, theta power seemed to upregulate over time after the injury.

Virtual reality paradigms can be used to challenge balance control. Virtual reality environments facilitate stimulus control, and stereoscopic vision allows participants to perceive motion-in-depth. They also allow the deployment of standardized and reproducible protocols. Previous studies have shown that virtual reality paradigms can challenge balance control, resulting in increased postural sway[61], center of pressure (COP) displacement[62], and modifications in ground reaction forces[63]. Horlings et al. (2009) comparing three visual conditions: eyes closed, eyes open, and virtual reality. The authors demonstrated an increase in postural sway with the latter. Sandri Heidner et al. (2020) tested a fore-and-aft sinusoidal room displacement virtual reality environment with varying frequencies and displacements, under the eyes open, eyes closed, and virtual reality conditions. They did not find increased balance sway under any condition for any of the frequency-amplitude pair but found that COP velocity and approximate entropy varied at a frequency of 5 Hz and an amplitude of 0.1-0.2 meters, suggesting that motor control strategies can be challenged in a life-like virtual reality environment.

In this research we sought to compare the effects of somewhat hard-to-hard physical exertion and the symptoms of acute concussion on brain activity by submitting participants to a series of balance perturbation conditions. We separated the groups between concussed and non-concussed and opted to test the baseline of concussed participants against the post-exertion state of non-concussed participants. We chose not to submit concussed participants to the bout of physical exertion due to uncertainties regarding their actual level of recovery. Although they had all been cleared to return to activities, recovery metrics are often inaccurate[64,65]. It was our first hypothesis that brain activity would be different between physically exerted and concussed participants. More specifically, we expected to find a higher alpha and theta spectral power in healthy controls soon after a somewhat hard-to-hard exertion protocol when compared to baseline and to concussed participants. Our specific aim was to investigate the presence of neural signatures that could differentiate between a concussive state and a fatigue state. Our hypothesis was that spectral power of cortical activations would be different between non-concussed participants in a fatigued state and concussed participants.

Methods

This research was performed in accordance with all regulations specified by the Internal Review Board of East Carolina University (UMCIRB 17-000797).

Participants

The study cohort was comprised of thirty-two (N = 32) healthy, non-concussed, young adults, and individuals recovering from mTBI. All healthy participants (n = 15) were repeatedly tested under normal and balance impaired conditions. This group was comprised of collegiate athletes, ROTC cadets, and law enforcement officers. All participants recovering from mTBI (n = 17) were tested once. Due to the extenuating nature of the exertion protocol, it was deemed safer to only test their baseline. Also, some concussed participants did not meet the minimum physical activity requirements to be included in the fatigue protocol. For non-concussed participants, inclusion criteria were designated as healthy young males and females aged between 18 and 35 years. For this project, the term healthy was defined as having no other current or previous neurological pathology that would interfere with postural stability during standing. All healthy participants exercised regularly (30+ minutes of vigorous physical activity 3+ times per week), had experience carrying a heavy backpack, and had no exercise counter indications such as cardiac issues or asthma. Additionally, the term healthy also referred to the lack of systemic disease that alters the ability of participants to participate in activities of their choice. Specific exclusion criteria included: (1) a history of stroke or neurodegenerative disease, (2) lower extremity neuromuscular pathology, (3) lower extremity orthopedic pathology, and (4) ocular or neurological abnormalities that impact visual function. These exclusion criteria were designed to prevent extraneous factors from confounding the neural activation and behavioral patterns related to balance.

Fatigue Protocol

A group of healthy young adults had their balance perturbed by a whole-body fatigue protocol. Physical fatigue was induced by having participants perform a 30-minute walk on an inclined treadmill (1.9 m/s) while wearing a weighted backpack (27 kg). Based on past work in our laboratory this represented somewhat hard-to-hard exercise. This load can be sustained for 2 hours but will induce substantial fatigue in 30 min[66]. To ensure participants stay in the desired range of intensity, exertion was assessed through several means: subjective level of exertion through Borg's RPE scale[67], heart rate was monitored using a polar monitor (Polar Electro, Lake Success, NY), the talk test[68] was used to ensure that the participants maintained their exertion level below ventilatory threshold. Exercise intensity (pace, incline) were adjusted to keep all participants at a somewhat hard-to-hard exercise intensity (Borg:12-14, heart rate: 50-70% of max HR, talk test: able to talk, but not sing) After the exercise, a general measure of fatigue was obtained with the Visual Analog Scale[69]. The objective of this protocol was to cause some level of physical fatigue, not complete exhaustion. Fatigue induced changes in sway have been shown to return to baseline after 20 minutes of rest[70], so balance measurements were collected within this period.

Conditions

Participants were assessed under a variety of conditions: eyes-closed (EC), eyes-open (EO), single leg (SL), mental distraction (SS), unstable surface (US), virtual reality-induced optical flow (VR), and virtual reality baseline (VB). During the single leg condition, participants stood on their dominant leg only. The mental distraction task consisted of counting down backwards in decrements of seven. The unstable surface condition was achieved by having participants stand on a foam pad. The virtual reality-induced optical flow consisted of a lifelike 3D replica of the laboratory inside a virtual reality environment; the virtual environment was moved fore and aft with an amplitude of 0.2m and 0.5 Hz[30]. The virtual reality baseline consisted of quiet standing while inside the virtual reality environment. The environment was developed in Unity (Unity Technologies, San Francisco, CA) and deployed using the Oculus RIFT virtual reality goggles (Oculus RIFT, Menlo Park, CA).

Electroencephalography

For participants in the Fatigue group, EEG was measured pre- and post-fatigue. For participants with mTBI, EEG was only measured once. Eye movements were recorded with electrodes placed above and below the left eye to capture electrooculographic (EOG) activity. Data acquisition was performed using a right ear reference at a sampling rate of 1KHz and filtered at DC-100 Hz. The left ear was also recorded and used (offline) to create a linked ear reference. Each trial onset provided a unique marker in the EEG record. Offline, a low pass filter (1 Hz) was applied. Data was re-epoched time zero through 20 seconds of the trial. Time zero (0 ms) was established as the beginning of the epoch, and each epoch was baseline corrected over the interval from 0 ms to 500 ms. Epochs were sorted into unique trial variants corresponding to the balance challenge. An autoregressive model was used to remove any blinks or other ocular artifact from the data based on the EOG signal[71,72]. Any trials with residual artifacts were visually identified and removed from analysis.

Testing Procedure

Upon arrival at the lab, participants were seated in a chair and any hair care products were removed from the hair with an alcohol-saturated cotton pad. The forehead was prepared by wiping the area with a cotton pad and a solution of pumice and Vitamin E, thereby removing any residual oil and dirt from the skin. Then, participants were fitted with a 64-channel EEG cap (Compumedics Neuroscan, Charlotte, NC) to record neural activity using SynampsRT (Compumedics Neuroscan, Charlotte, NC). Once the cap was in place and properly aligned, the scalp under each electrode was prepared by first gently abrading the skin using the wooden end of a standard cotton swab with pumice and Vitamin E to reduce impedance to the electrode, and then inserting a conductive gel with a 16-gauge blunt needle.

Once participants were prepared, measurement of standing balance were conducted across three trials for all the challenges mentioned above, and quiet standing with no challenges. EEG was recorded for each test. For VR-based challenges, an output from the controlling computer was sent to the EEG acquisition computer to mark the onset of each trial. All trials lasted 30 seconds for each condition[73], after which the participant received a brief rest period before starting the next trial. After the initial bout of trials was performed, participants in the non-concussed group were transitioned to a treadmill, without removing the EEG cap, to perform the fatigue protocol. At the end of the fatigue protocol, participants were then seated, and all EEG electrodes were checked for proper impedance. Electrode preparation was repeated as needed. This process was kept under 10 minutes, after which, participants underwent a complete bout of trials through all conditions, identical to their baseline testing.

Data Analysis

Data were inspected for normality using the Z_{skewness} and Z_{kurtosis} scores[74,75]. The normality tests had a level of significance set at $\alpha = .001$. Non-parametric data sets were treated with a natural logarithmic (Ln) function and re-tested for normality. Two four-way ANOVAs were conducted to investigate the differences within and between groups. The dependent variable was mean natural log of spectral power. The independent variables were condition (EC, EO, SS, SL, US, VR, VB), time/group (pre-/post-fatigue, post-fatigue/concussed), brain region (Frontal, Motor Cortex, Temporal, Central Sulcus, Sensorimotor Cortex, Parietal, Occipital), and frequency band (alpha, theta). The first univariate design was strictly within-subjects repeated-measures model and analyzed the pre- and post-fatigue protocol in the non-concussed group across all conditions, brain regions, and frequency bands. Post-hoc analysis was done through a means and confidence intervals approach. The second univariate design was a between-subjects comparison of the post-fatigue non-concussed group and the concussed group baseline, also across all conditions, brain regions, and frequency bands. Tukey's HSD post-hoc test and equality of means with Bonferroni correction were used to investigate main effects and interactions. The level of significance for these tests was set at $\alpha = .05$.

Results

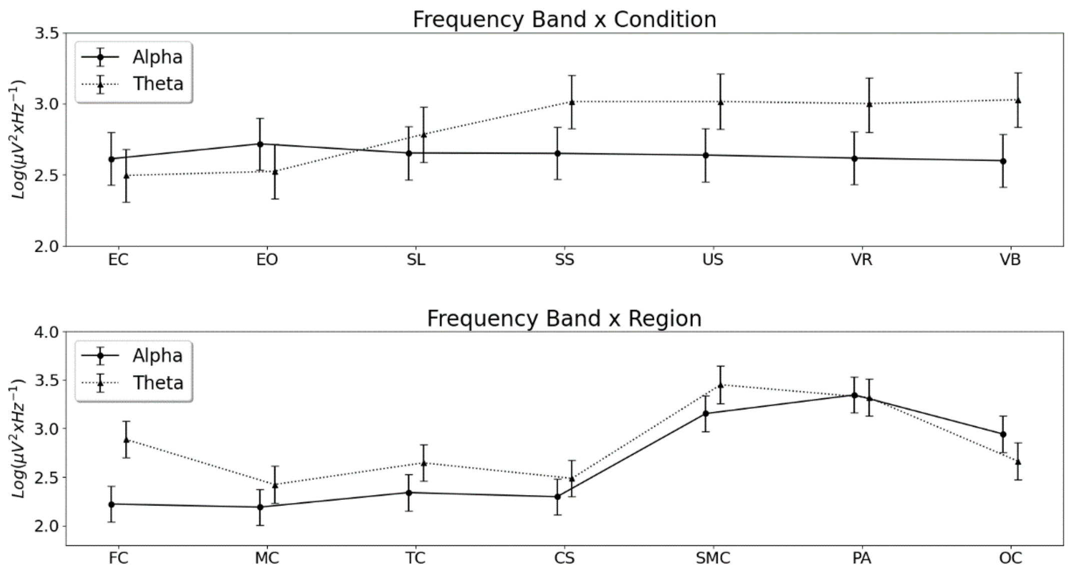
Non-concussed: pre- and post-fatigue EEG

A total of thirty-two ($N = 32$) experimental participants were enrolled in this research. Fifteen participants ($n = 15$) completed the fatigue protocol. After visual inspection, data processing, and removal of outliers, there were 4277 (94.0 %) valid and 273 (6.0 %) missing data points. Spectral power had a textbook exponential distribution and was normalized by taking the natural logarithm of the data points. Natural log spectral power (LnP; $M = 2.59$, $SD = 1.54$) was positively skewed ($Skew/SE\ Skew = 17.32$, $p < .001$, two-tailed) and mesokurtic ($Kurt/SE\ Kurt = 2.57$, $p = .002$, two-tailed).

A four-way repeated measures ANOVA was conducted to investigate the effects of Time (baseline, fatigue), Condition (EC, EO, SL, SS, US, VR, VB), Region (Frontal, Motor Cortex, Temporal, Central Sulcus, Sensorimotor Cortex, Parietal, Occipital), and Bandwidth (Alpha, Theta) on spectral power. The test of within-subjects effects revealed a significant main effect of Time, $F(1, 4) = 7.82$, $p = .049$, $\eta_p^2 = .662$, and significant interactions between Condition x Bandwidth, $F(6, 24) = 8.84$, $p < .001$, $\eta_p^2 = .689$, Region x Bandwidth, $F(6, 24) = 6.00$, $p = .001$, $\eta_p^2 = .600$, and Condition x Region x Bandwidth, $F(36, 144) = 2.24$, $p < .001$, $\eta_p^2 = .360$. Estimated marginal means and 95% confidence intervals are shown in Figure 3.1. A pairwise comparison of

Time was made using Tukey's HSD pots-hoc test. Spectral power (M_{pre} = 2.38, SD_{pre} = .19) increased by approximately 27.3% (M_{post} = 3.03, SD_{post} = .32) when participants were fatigued.

Figure 3.1. *Estimated Marginal Means of Band Power Across Conditions and Brain Regions: Non-concussed pre- and post-exertion*



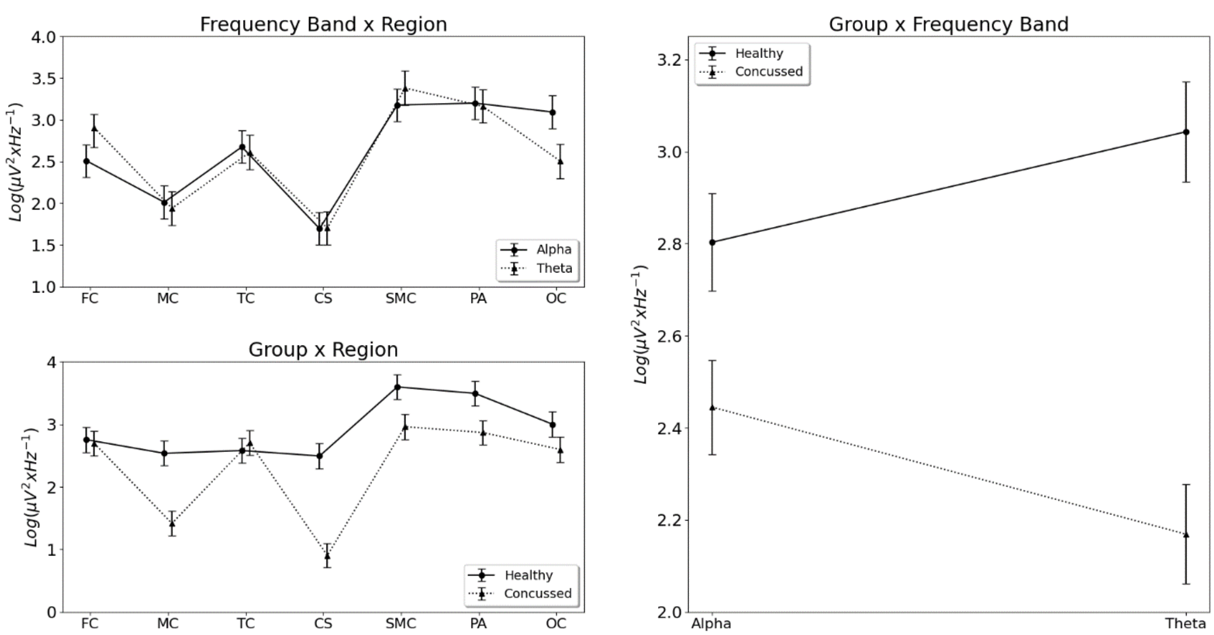
Note. Graphs show the relationship between frequency bands (Alpha, Theta) and condition (top), and brain region (bottom) in the non-concussed group. Error bars represent the 95% confidence interval. EC: eyes closed; EO: eyes open; SL: single leg; SS: subtraction of sevens; US: unstable surface; VR: virtual reality intervention; VB: virtual reality baseline; FC: frontal cortex; MC: motor cortex; TC: temporal cortex; CS: central sulcus; SMC: sensorimotor cortex; PA: parietal cortex; OC: occipital cortex.

Non-concussed post-fatigue and concussed EEG

Seventeen participants (*n* = 17) completed the mTBI protocol. Their data was combined with the post-fatigue protocol (*n* = 15) for comparison. After visual inspection, data processing, and removal of outliers, there were 2802 (92.3 %) valid and 236 (7.7 %) missing data points. Spectral power was normalized by taking the natural logarithm of the data points. Natural log spectral power (LnP; *M* = 2.60, *SD* = 1.57) was positively skewed (*Skew*/*SE Skew* = 10.69, $p <$ .001, two-tailed) and mesokurtic (*Kurt*/*SE Kurt* = 1.14, *p* = .127, two-tailed).

A two-way univariate ANOVA was conducted to investigate the effects of Group (fatigue, mTBI), Condition (EC, EO, SL, SS, US, VR, VB), Region (Frontal, Motor Cortex, Temporal, Central Sulcus, Sensorimotor Cortex, Parietal, Occipital), and Bandwidth (Alpha, Theta) on spectral power. Levene's Test of Equality of Error Variances showed that the assumption of heteroskedasticity was not met, $F(195, 2606) = 1.98$, $p < .001$. The test of between-subjects effects revealed a significant main effect of Condition, $F(6, 2606) = 8.08$, $p < .001$, $\eta_p^2 = .018$, and significant interactions between Region x Bandwidth, $F(6, 2606) = 4.64$, $p < .001$, $\eta_p^2 = .011$, Region x Group, $F(6, 2606) = 17.34$, $p < .001$, $\eta_p^2 = .038$, and Bandwidth x Group, $F(1, 2606) = 22.79$, $p < .001$, $\eta_p^2 = .009$. Estimated marginal means and 95% confidence intervals are shown in Figure 3.2. A pairwise comparison of Condition was made using Tukey's HSD pots-hoc test. Homogenous subsets showed that spectral power was lowest for EC, EO, SL, and SS; US power was lower than VR and VB; VR power was lower than VB.

Figure 3.2. *Estimated Marginal Means of Frequency Band Power: Fatigued v. Concussed*

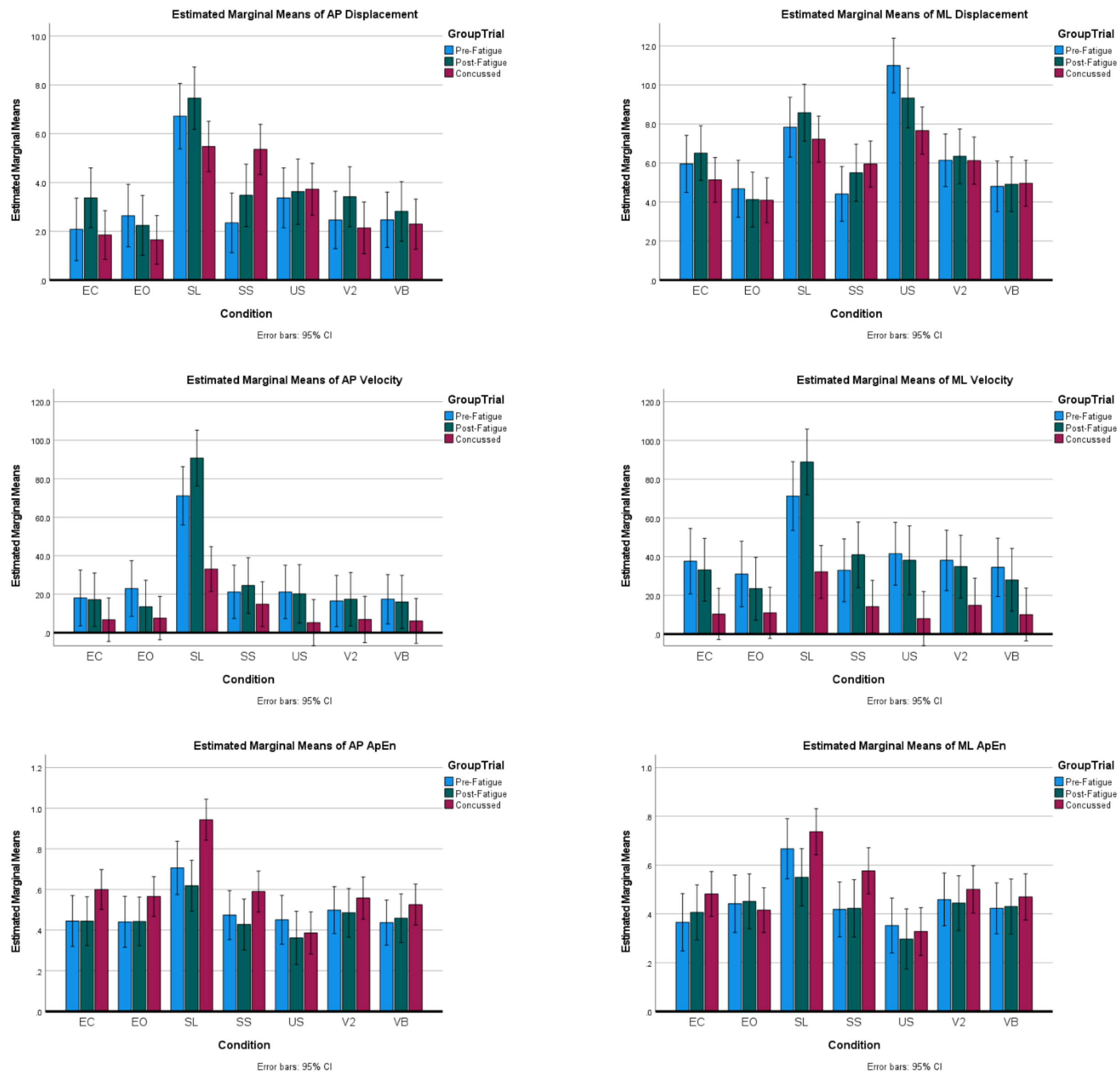


Note. Error bars represent the 95% confidence interval. FC: frontal cortex; MC: motor cortex; TC: temporal cortex; CS: central sulcus; SMC: sensorimotor cortex; PA: parietal cortex; OC: occipital cortex. Top left: depiction of overall typical brain function without group discrimination. Bottom left: frequency-independent cortical power across groups. Right: whole brain alpha and theta power differences between non-concussed and concussed groups.

Balance Metrics

A two-way MANOVA was conducted to investigate the effects of balance metrics (AP COP displacement, ML COP displacement, AP COP velocity, ML COP velocity, AP COP displacement approximate entropy, and ML COP displacement approximate entropy) DVs on group (non-concussed pre-fatigue, non-concussed post-fatigue, and concussed) and condition (EC, EO, SL, SS, US, VR, VB) IVs. Box's test of equality of covariance matrices showed that the assumption of homogeneity of variances and covariances was not met, $F(420, 25306.49) = 3.15$, $p < .001$. Wilk's lambda revealed a significant Group x Condition interaction, $F(72, 1398.59) = 1.43$, $p = 0.011$, $\eta_p = .063$. Levene's test of equality of error variances was significant for all balance metrics, all $p < .001$. The tests of between-subjects effects showed Group x Condition interactions in AP COP displacement, $F(12, 261) = 2.02$, $p = .022$, $\eta_p = .085$, and AP COP velocity, $F(12, 261) = 1.98$, $p = .026$, $\eta_p = .084$. There were also significant main effects of Group on ML COP velocity, AP COP displacement ApEn, and ML COP displacement ApEn, [$F(2, 261) = 29.91$, $p < .001$, $\eta_p = .186$; $F(2, 261) = 11.01$, $p < .001$, $\eta_p = .078$; $F(2, 261) = 3.68$, $p = .026$, $\eta_p = .027$, respectively], as well as significant main effects of Condition on ML COP displacement, ML COP velocity, AP COP displacement ApEn, and ML COP displacement ApEn [$F(6, 261) = 19.51$, $p < .001$, $\eta_p = .310$; $F(6, 261) = 9.33$, $p < .001$, $\eta_p = .177$; $F(6, 261) = 10.17$, $p < .001$, $\eta_p = .190$; $F(6, 261) = 8.90$, $p < .001$, $\eta_p = .170$, respectively]. Means and standard deviations are show on Figure 3.3.

Figure 3.3. Means and Standard Deviations of Balance Metrics Comparing Non-concussed Pre- and Post-exertion, and Concussed Participants



Note. AP: antero-posterior; ML: mediolateral; EC: eyes closed; EO: eyes open; SL: single leg; SS: subtraction of sevens; US: unstable surface; VR: virtual reality intervention; VB: virtual reality baseline; Displacement unit is meters; Velocity units is mm$*$s^{-1}; Approximate Entropy (ApEn) is a probabilistic range between 0-1.

Discussion

In this project, we sought to investigate and better understand the relationship between concussion, somewhat hard-to-hard physical exertion, and modulation of alpha and theta power spectra on seven major regions of the brain. Seven different conditions were used to challenge the nervous system in four diverse ways: optical flow restriction, mechanical balance perturbation, cognitive loading, and virtual reality induced optical flow. Our initial hypothesis was that non-concussed participants who were subject to the exertion protocol would have higher alpha and theta spectral power soon after their bout of physical activity when compared to concussed participants.

Non-concussed: pre- and post-exertion

The significant main effect of time and subsequent pairwise comparison confirmed that spectral power of both theta and alpha bands was higher immediately post-exertion. In addition to this, when the frequency bands were analyzed in relation to the several stimuli conditions, theta power was greater than alpha power during the mental task of subtraction of sevens, the physical task of unstable surface, and the optical flow tasks of virtual reality baseline and virtual reality perturbation. When analyzed across brain regions, theta power was greater than alpha power in the frontal cortex, with no differences observed between theta and alpha power in the motor cortex, temporal cortex, central sulcus, sensorimotor cortex, parietal, or occipital lobes in non-concussed participants. Further analysis revealed that alpha power in the parietal lobe was greater than in the frontal cortex, motor cortex, temporal cortex, and central sulcus across all conditions. Also, alpha power in the sensorimotor cortex was greater than in the frontal, motor, and temporal cortexes during the single leg, subtraction of sevens, unstable surface, virtual reality baseline, and virtual reality perturbation conditions.

Alpha and theta rhythm are related to cognitive processing[76,77]. Increases in alpha and theta power were observed as a result of the exhaustion of cognitive resources[78,79]. As expected, non-concussed participants had an increase in alpha and theta rhythm power after their bout of exertion, suggesting some level of exhaustion of their cognitive resources. Moreover, this cognitive bottleneck was present during cognitive and balance-related motor tasks, and virtual reality induced optical flow perturbations. Since an increase in alpha power in the parietal lobe has previously been linked to a greater demand for internal processing, i.e., when bottom-up processing is prevented[80], it would be fair to assume that the combination of mental fatigue and the different conditions can interfere with the ability to perform sensory-intake tasks. Also of note is the increase in theta power during this mentally fatigued state. Cavanagh & Frank (2014) reported an increase in theta band activity in the mid-frontal cortex when subjects needed to exert cognitive control over a task. In another study, prefrontal theta power increase was associated with response inhibition[82]. This may indicate an interference with goal-driven behavior. As such, we can safely assume that the mental fatigue induced by a somewhat hard-to-hard bout of physical activity is sufficient to disrupt the normal neurocognitive processing of non-concussed individuals.

Concussed and Post-exertion Non-concussed

The concussed group had an overall lower spectral power for both alpha and theta when compared to the post-exertion group. This is in line with some previous research[22,24]. Decreases in alpha and theta power have been previously associated with active processing in cortical systems[83,84]. More specifically, alpha and theta tend to either be suppressed in the activated brain region or incited in the contralateral brain region[85]. Also, alpha has been found to be inversely related to grey matter blood flow while theta was shown to have the opposite behavior[86]. Our results agree with these findings but contrast with others. Previous studies have found that theta and alpha were higher in temporal and deep-grey regions of mTBI patients when compared to non-mTBI[87], and an increase in theta power during the first six months post-injury[29]. However, Dunkley's study was performed in resting state as opposed to using mental or motor tasks. There seems to be a dichotomous behavior of alpha and theta spectral power in concussed patients depending on whether they are presented with a task or analyzed in resting state.

Theta and alpha spectral power were mostly the same across all brain regions, except for a theta power greater than alpha in the frontal cortex and a theta power lower than alpha in the occipital lobe. Decreased frontal alpha power was previously observed in concussed athletes compared to non-concussed athletes[88]. Conversely, alpha activity greater than theta activity in the posterior regions are expected in typical individuals[89]. However, in mTBI[90] and certain pathologies[91], alpha's predominance over theta decreases, presumably due to deficits in pre-synaptic cholinergic markers in the cerebral cortex. In our findings, overall spectral power was not different in the frontal or temporal cortexes when comparing concussed and non-concussed groups. However, it was overall lower in all other regions of concussed participants. The greatest differences were observed in the central sulcus and the motor cortex, respectively, followed by the sensorimotor cortex, parietal, and occipital lobes.

When we consider the whole cerebral cortex, the largest difference was observed in theta power, which was greater than alpha in the fatigued group, but lower than alpha in the concussed group. This reduction of theta power resulting in an increase of the alpha-theta ratio is related to residual symptoms of mTBI[92,93]. Conversely, while executing certain tasks, the alpha-theta ratio was lower in the exerted group. A decreased alpha-theta ratio has been previously reported as an indicator of decreased mental processing capacity associated with degenerative conditions, such as Alzheimer's disease[89]. However, these changes in alpha-theta ratio between non-concussed pre- and post-exertion occurred only during task execution. This decrease in processing during mental fatigue is expected.

Overall, we have found a neural signature that can differentiate between two disparate groups of people: concussed and post-exertion non-concussed. The most significantly different neural signatures were found in (i) a reduced overall spectral power on the motor cortex and central sulcus of concussed participants, and (ii) in the increase in theta spectral power in an exerted state compared to the reduction of theta spectral power in a concussed state. Future research should likely be aimed at differentiating between perturbation paradigms to ascertain which ones are specifically responsible for the variances in spectral power when assessing concussed participants.

Funding

This work was supported by the Office of Naval Research under Grant ONR - N000141712723.

Disclosure Statement

The authors report there are no competing interests to declare.

Chapter 4: Long-lasting oculomotor and postural control impairment after mTBI

Gustavo Sandri Heidner[1], J.C. Mizelle[1], Zachary J. Domire[1], Stacey Meardon[2], Brian Sylcott[3], Nicholas P. Murray[1].

Department of Kinesiology[1], Department of Physical Therapy[2], Department of Engineering[3], East Carolina University, Greenville, NC, USA

Abstract

Concussions often result in short-lived to long-lasting neurological function impairment, with symptoms appearing immediately, and possibly deteriorating into permanent neural damage. Several efforts have been made to quantify the incidence concussions and to improve diagnostic methods, which are still largely inconclusive and not always accurate. An absence of specific neuromuscular markers compromises diagnostic ability and reliability. For that purpose, we chose to investigate the neural correlates of oculomotor metrics (eye tracking) and corticomuscular coherence (EEG-EMG) metrics when participants are submitted to a virtual reality-implemented optical flow paradigm. A cohort of 13 concussed and 20 non-concussed participants were screened for levels of physical activity before undergoing a secondary cognitive task in virtual reality environment. Eye-tracking and corticomuscular coherence metrics were compared between groups. Both groups performed similarly in the eye-tracking task but differed significantly in corticomuscular coherence metrics. The concussed group had a significant increase in beta and low gamma band correlations between the frontal and sensorimotor cortexes and their contralateral soleus and tibialis anterior muscles.

Introduction

Concussions (mTBI) occur when an impulsive force is transmitted to the head, resulting in short-lived to long-lasting neurological function impairment[3]. Symptoms present themselves immediately, and may deteriorate into permanent neural damage[4]. Among those symptoms, loss of concentration, fatigue, oculomotor impairments, and dizziness are common and can be present for at least one year posttrauma[5]. Given the severity and the prevalence of mTBI symptoms, several efforts have been made to quantify the incidence and to improve diagnostic methods[6]. However, the methods to assess impairments due to concussions are still largely inconclusive and not always accurate[7–10]. Since posttraumatic mTBI effects do not yet have specific neuromuscular markers, the ability and the reliability of diagnostics is compromised. To better assess the long-term impairments of mTBI, it is imperative to discover and discretely define potential biological markers associated with it. For that purpose, we chose to investigate the neural correlates of oculomotor metrics (eye tracking) and corticomuscular coherence (EEG-EMG) metrics when participants are submitted to a virtual reality-implemented optical flow paradigm.

A power-based analysis of the EEG signal targets certain frequency bands (i.e., delta = .5-4 Hz; theta = 4-8 Hz; alpha = 8-12 Hz; beta 12-30 Hz; low gamma = 30-50 Hz; high gamma = 50+ Hz) that can be associated with activity in certain areas of the brain, e.g., frontal cortex and sensorimotor cortex. This type of analysis describes the magnitude of brain activity within the EEG frequency bands[19]. The frontal cortex is where higher processing of sensory information occurs before voluntary input is sent to be integrated and translated into movement commands in the sensorimotor cortex. The frontal cortex is also responsible for managing selective attention and distinguishing between objects, making it a prime target for investigation when visual choice tasks are present. Temporal correlation or coherence-based analyses are performed to investigate connectivity between areas of the brain. A higher signal correlation is found for time series that co-vary together[21], and this is believed to be evidence of neural communication.

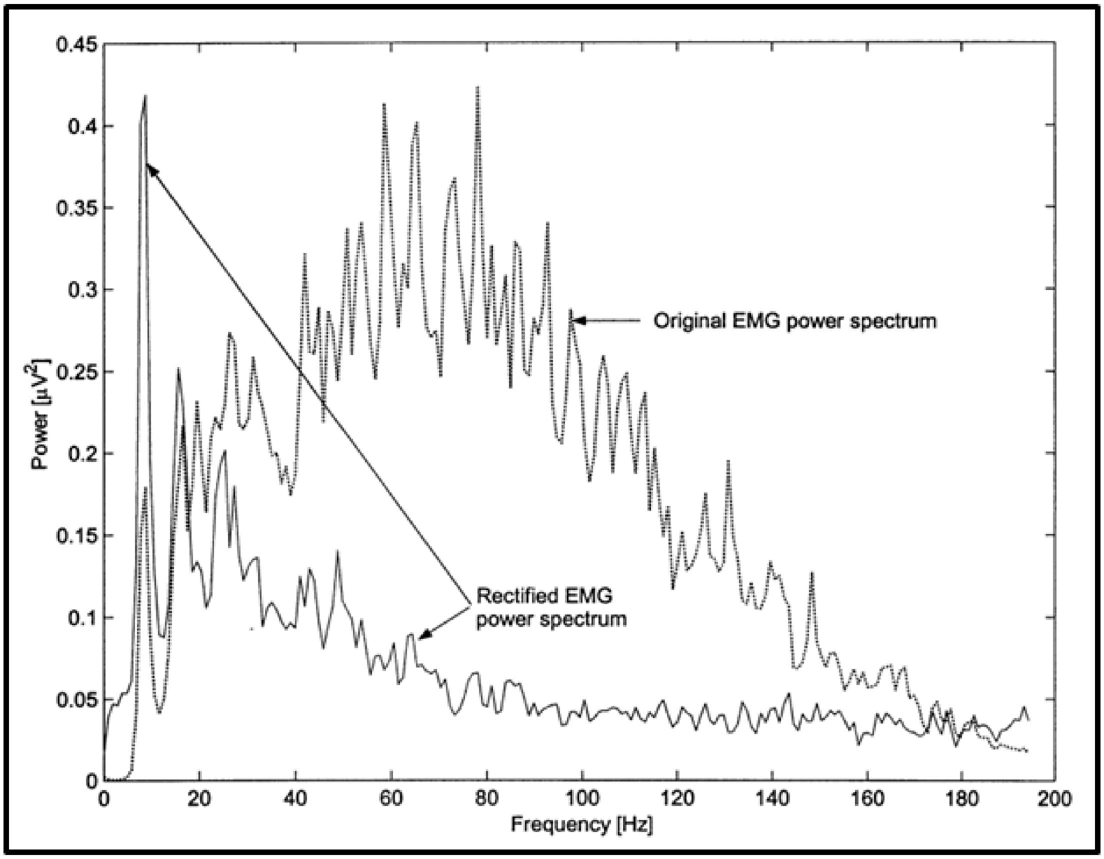
In addition to EEG, electromyography is a non-invasive electrophysiological technique also used to study the peripheral consequences of mTBI. Surface EMG is employed to record and evaluate electrical activity produced by skeletal muscles[94] and measures the electric potential of muscle fibers, from which inferences of functionality can be drawn. Electromyography is in the clinical setting to diagnose peripheral neuromuscular conditions, and in kinesiology and motor control research, since it provides information on the time, frequency, velocity, and delay of muscle activation[94]. It is a valuable tool in the study of corticomuscular coherence.

In a bipolar configuration of sEMG, the two electrodes measure the summation of the differential electric potential of each muscle cell membrane polarization and depolarization that occurs at each discrete point in time. This muscle cell membrane oscillation in electric potential is dependent on the stimulation of cholinergic receptors following the motor neuron nerve impulses that arrive at the neuromuscular junction. If a sufficient potential is generated, voltage-gated sodium channels propagate the depolarization into the skeletal muscle cell[95], and through the T-tubules. Hence, the magnitude of the sEMG signal depends on the synchronization of membrane potentials. This synchronization is a key factor in the generation of muscle force[96], and is dependent on the integrity of the neuromuscular pathway. Transient conditions, such as fatigue[97], as well as some chronic neurological conditions, like Parkinson's disease[98], can alter the frequency synchronization of skeletal muscle cells.

Mathematically, coherence is an extension of Pearson correlation coefficient in the frequency domain and defined as cross spectra normalized by auto spectra[99]. Corticomuscular coherence is the temporal correlation between brain activity, measured by electroencephalography, magnetoencephalography, or local field potentials, and muscle activity, measured by surface electromyography[99]. The temporal synchronization between waveforms suggests the existence of a source-target coupling, represented, in this case, by the brain (source) and the muscle (target). It is yet unknown how mTBI affects corticomuscular coherence. The general hypothesis is that temporal desynchronization may be present if there is significant neural damage post-trauma.

An increasing, albeit low, amount of studies have identified beta- and gamma-band corticomuscular coherence between the brain and lower-extremity muscles[100–102], but studies do not typically investigate brain waves in frequencies above 30 Hz (i.e., low- and high-gamma)[103–105]. This is particularly important because data suggest that although beta-range corticomuscular synchronization has been extensively investigated during steady-state motor output, a significant shift from beta- to gamma-range synchronization occurs when the force output is dynamic[105]. This phenomenon has also been demonstrated during corticomuscular synchronization of the lower-limbs, with isometric contractions favoring beta-range oscillations, while isotonic contractions favor gamma-range oscillations[103]. Moreover, a majority of unrectified EMG activations occur between 40-100 Hz. This range changes (see Figure 4.1) when EMG signal is rectified. Although there is still an intense debate over the need to rectify[106] or to not rectify[107] EMG waveforms, there are evidences that rectification of the EMG waveform can cause a substantial decrease in signal power over higher frequencies, along with an increase in signal power on lower frequencies[108].

Figure 4.1. Comparison of Spectral Power Between Rectified and Non-rectified EMG

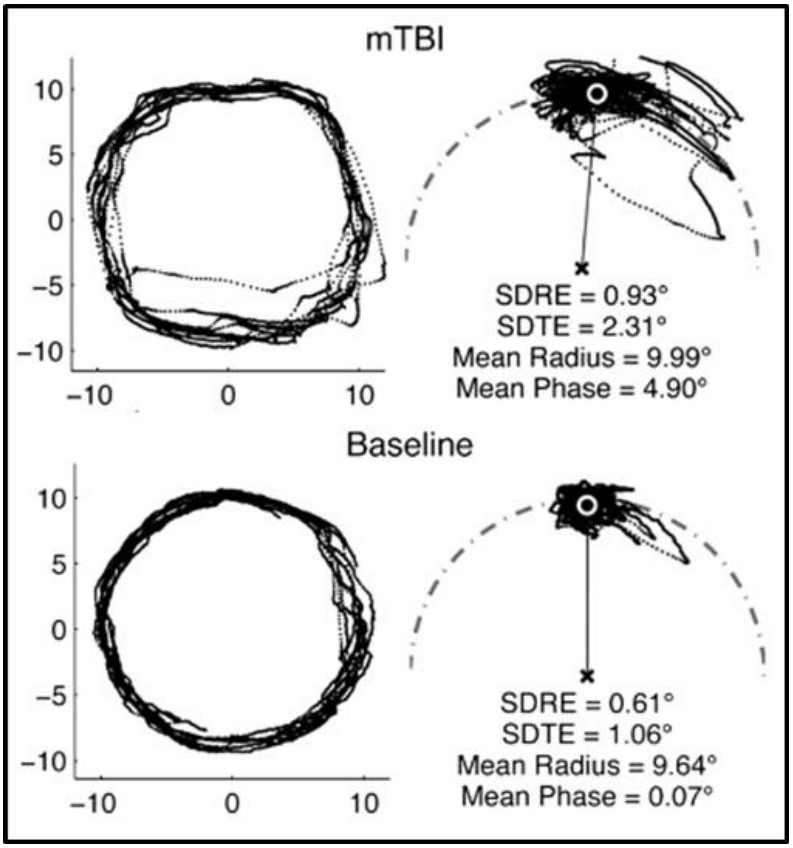


Note. A substantial portion of unrectified EMG activations are found between 12-90 Hz, the same range shared by beta (12-30 Hz), low gamma (30-50 Hz) and high gamma (50-90 Hz) frequency bins.

Even though corticomuscular coherence is a good method to study interactions between the cortex and relatively large peripheral muscles, it is impractical in the assessment of oculomotor function. The three motor nerves responsible for eye movement (Cranial Nerves III, IV, and VI) control the recti and oblique muscles, which are responsible for vertical and longitudinal translation, and rotation of the eye. Since non-invasive EMG cannot reach those muscles, researchers tend to use eye tracking techniques to investigate abnormalities in visuomotor control.

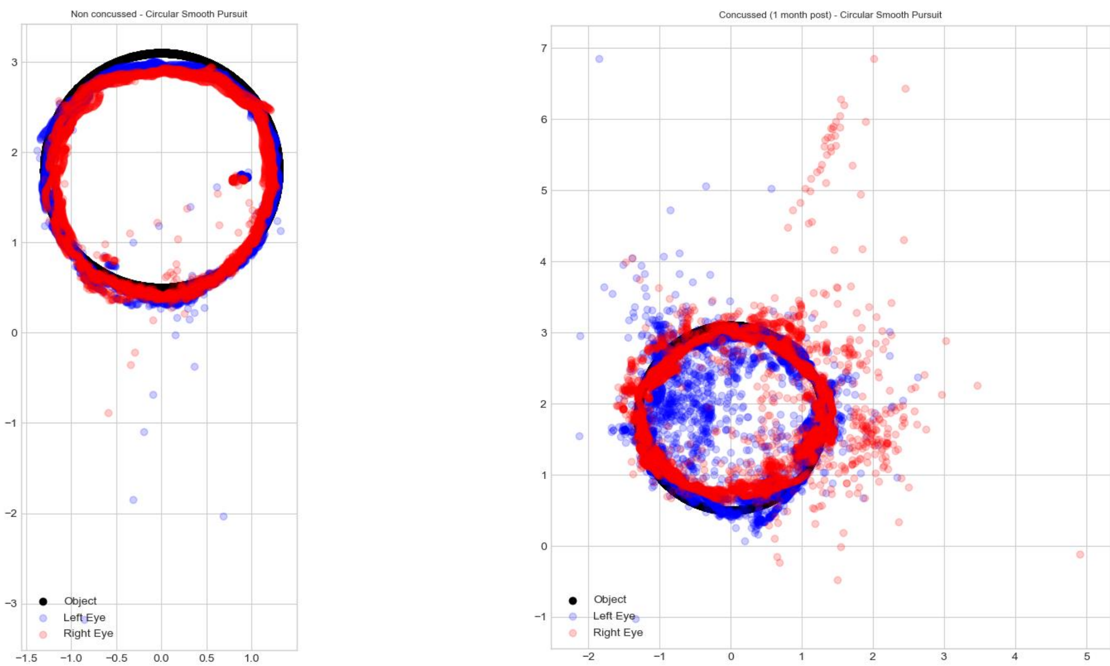
There are four types of eye movements: smooth pursuit, saccade, vergence movements, and vestibulo-ocular movements. Smooth pursuit are slow voluntary eye movements with the objective of keeping the stimulus on the fovea[38]. Smooth pursuit can occur in a linear[39] or circular fashion, or a combination of both[40]. Saccades are ballistic movements of the eye when they change the fixation point. They can be of small or large amplitude and can happen voluntarily or involuntarily. Involuntary saccades occur as a reflex response when the eyes are open. Saccadic movements have a refractory period (15-100 ms) when the eyes start to move and cannot change direction after movement has started. In that sense, they depend on an estimation of the target's position. If the target changes position during the saccade, another saccade has to be made to correct the error[38]. Given that saccades are controlled by the frontal cortex, this second saccadic movement is called an anti-saccade and can be used as a gross estimation of dysfunction of the frontal lobe[109]. Circular smooth pursuit data of subjects that had sustained an mTBI within the past two weeks was compared to subjects that had not sustained an mTBI. The circular tracking ability of the mTBI subjects was significantly impaired when compared to the controls[110] (Figure 4.2, Figure 4.3).

Figure 4.2. Circular Smooth Pursuit Trace: Concussed and Non-Concussed.



Note. From Maruta et al., 2014; Two graphs depicting the differences in circular smooth pursuit traces (left) and target frame cue fixation (right) between concussed (top) and non-concussed (bottom) participants; SDRE: standard deviation of radial error; SDTE: standard deviation of tangential errors.

Figure 4.3. Pilot Data – Circular Smooth Pursuit Trace: Concussed and Non-Concussed



Note. Data plot of circular smooth pursuit task performed in virtual reality, featuring individual eye tracking. Red dots: right eye; Blue dots: left eye; Black line: cue trajectory. Concussed participant depicted on the right-side graph. Non-concussed participant depicted on the left-side graph. Axes units are meters.

The investigation of abnormalities in saccadic movements after brain injury is interesting because of their reliance on coordination and timing of the neural pathways between the frontal lobe, basal ganglia, superior colliculus, and cerebellum[35]. This analysis may be an important tool for diagnosing post-concussion syndrome and acute mTBI, as poorer saccadic movements may indicate injury in those areas. An interesting point is that impaired saccadic movements are associated with suboptimal brain function beyond the influence of depression, malingering, and intellectual ability in post-concussion syndrome subjects[36]. Regarding mTBI specifically, Cifu et al. (2015) present data to support the hypothesis that mTBI subjects, when compared to controls, have higher initial and final position error, as well as lower predicted velocity and acceleration, with increased predicted duration of saccadic movements when performing an horizontal displacement task[35]. It stands to reason that cortical and visuomotor control impairments stemming from a concussive event can influence other processes that are dependent on vision and higher neural processing, such as making correct visual distinction between similar cues and making decisions based on that distinction. During this process of identifying the cue and making a decision, several variables can be extracted from eye-tracking metrics, such as the time spent actively looking at the cue (lingering time), the time it takes to visually react to the cue (visual reaction time), the time to process the information and provide a response after the presentation of the cue (motor reaction time), how close their gaze gets to the center of the target (accuracy), and for how long do they accurately look at the center of the cue (a composite score of accuracy and lingering time).

Decision-making is a process that happens in a situation in which some of the goals, constrained by the environment and personal capacity, and consequences of the possible actions are not known precisely[111]. In this case, a constraint may be the configuration of the field during a game at a certain point in time, or the athlete's perception of how fast he can move his body out of the way of an incoming player. In physical activity and sports, this paradigm is slightly different than in controlled laboratory situations. Given that an observer constructs most of his knowledge about environmental constraints when he is stationary in the lab, this knowledge might not be precise when the environment in which a decision must be made is dynamic[112]. Therefore, exposure to practice in a dynamic task may help to generate a better pool of possible responses for certain situations that tend to repeat themselves or that are similar. However, it is also not only the dynamic nature of the environment or task, but the number of choices and uncertainty about the constraints that tend to increase lag in response time or induce a 'wrong' solution to the problem at hand, which adds complexity to the decision-making process[113–115]. When visual perception is negatively affected during acute mTBI and post-concussion states, it can influence the decision-making process and play an important role in the performance outcome during physical activity. This hypothesis is supported by data on animal[116] and human[117,118] models, indicating a decreased decision-making ability after sustaining a traumatic brain injury. Cardoso et al. (2014) showed that not only did TBI patients score worse on the Iowa Gambling Task (IGT) when compared to healthy controls, but also that there were no score differences between mild and severe TBI participants[118]. Similarly, Levine et al. (2005) had also previously reported the lower performance of TBI participants on the IGT, and no difference in test scores between mTBI and severe TBI[117].

Besides the IGT, other common methods of testing decision-making capability are go/no-go and reaction time tasks[119,120]. Ho et al. (2018) showed that adolescents that have previously sustained a TBI and had symptoms of depression engaged the frontal areas of the brain to a greater extent than those that had not had a TBI, but they did not observe any activity the prefrontal cortex, which may be indicative of disruption of frontal networks[119]. This increased activity in the frontal regions in patients with depression subjected to emotional tasks is believed to occur due to their need to disengage from emotional processing in order to allocate resources towards the cognitive task at hand[121]. With a different design, Howell et al. (2017) demonstrated that children and adolescents with mTBI have lower performance on a go/no-go paradigm also had slower dual-task gait speed[120]. Furthermore, the lower dual-task gait speed was independently correlated with participants brain network activation, to which the authors suggest that motor and neural deficits may reflect the disruption of several abilities after concussion[120]. Virtual reality can be used as a method to deliver both oculomotor and choice reaction time paradigms that challenge the visual and vestibular system with the purpose of identifying markers of long-lasting effects of mTBI[43] or to assess residual executive disfunction[44] and balance impairments post mTBI in military personnel[45].

Despite the available evidence that corroborates abnormal eye control and neuromotor deficits during acute mTBI, the knowledge gap remains when subjects are asymptomatic (i.e., when they cannot be diagnosed as either acute mTBI or in post-concussive syndrome). It is still unclear for how long these abnormalities in visuomotor control and neuromuscular function can be detected after the symptoms of acute mTBI and/or post-concussive syndrome have subsided. Furthermore, aside from a single military cohort study that shows a higher prevalence of lower extremity injuries, there is a lack of knowledge about which motor control mechanisms may be related to these long-lasting effects of mTBI.

Although there are some data on the negative effects of mTBI on oculomotor ability and corticomuscular coherence of concussed subjects, there appears to be no study that have investigated the persistence of oculomotor ability decrease, and the link between corticomuscular coherence and balance impairments in this cohort. It is still unclear what role oculomotor function plays in the maintenance of postural control several years post-concussion. The purpose of this study was to investigate these long-lasting oculomotor impairments and corticomuscular correlates in mTBI participants compared to non-concussed controls over the course of 8 years. Our first hypothesis was that impaired oculomotor function would be detectable several years post-trauma. Our second hypothesis was that balance deficits would be related to changes in neural modulations observed in the frontal and sensorimotor cortexes.

Methods

This research was performed in accordance with all regulations specified by the Internal Review Board of East Carolina University (UMCIRB 20-000410).

Participants

The study cohort was comprised of thirty-three (N = 33, n = 13 concussed) young adults (M_{age} = 21.6 ± 3.0 years), with a BMI lower than 30, with normal or corrected-to-normal vision (i.e., glasses or contact lenses) that had or had not had a concussion in the past 8 years (M_{time} = 33.8 ± 26.0 months since last concussion). Concussion status, severity, and time since injury were determined by self-provided clinical record that came from a licensed clinical practitioner (e.g., physical therapist, athletic trainer, physician). Participants that did not meet the inclusion criteria were excluded. Participants were also excluded if they had visually obvious or self-reported (excluding mTBI): (i) current or previous neurological pathology that would interfere with the postural stability, (ii) history of stroke or neurodegenerative disease, (iii) lower extremity neuromuscular pathology, (iv) lower extremity orthopedic pathology, (v) ocular, auricular, or neurological abnormalities that impact visual and hearing function. These exclusion criteria were designed to prevent extraneous factors from confounding the neural activation and behavioral patterns related to balance.

Levels of Physical Activity

Epidemiological data shows that the majority (>54%) of concussions are sport-related[122]. In the 16–34-year-old group, sports were associated with over 85% of the concussive event[122]. Participants were asked to answer a questionnaire about their weekly levels of physical activity (IPAQ; Appendix B.2), which was used to match the groups. Participants were asked to answer a questionnaire about their weekly levels of physical activity (IPAQ; Appendix B.2). From the questionnaire, three types of physical activity were extracted: vigorous, moderate, and walking time. Data were reduced to reflect the number of weekly minutes spent doing vigorous, moderate, and walking activities.

Physical activity levels of participants were not normally distributed (Vigorous: *skew* = 1.26, *kurtosis* = 2.08; Moderate: *skew* = 1.02, *kurtosis* = .48; Walking: *skew* = 2.26, *kurtosis* = 5.31). Levene's test for equality of variances showed that the assumption of homogeneity of variance was met for vigorous physical activity (F = 1.86, p = .182), not met for moderate physical activity (F = 6.78, p = .014), and met for walking time (F = .01, p = .912). Independent samples t-tests showed no differences between groups in levels of vigorous physical activities, t(31) = -.14, p = .882, d = .053, moderate physical activity, t(16.68) = -1.75, p = .097, d = .705, or walking time, t(31) = -.43, p = .666, d = .155. Means and standard deviations are shown in Table 4.1.

Table 4.1. Weekly Time Spent in Physical Activities by Group

	Group	*N*	Mean	*SD*
Vigorous	Non-concussed	20	160.5	140.7
	Concussed	13	169.6	211.5
Moderate	Non-concussed	20	158.2	142.8
	Concussed	13	297.6	262.16
Walking	Non-concussed	20	62.0	88.6
	Concussed	13	74.6	67.8

Note. *N* = sample size; *SD* = standard deviation.

EEG

The g.Nautilus RESEARCH (g.tec medical engineering GmbH, Austria) wireless EEG with a 10-20 configuration 32 channel cap and gold-plated dry electrodes were used to collect cortical desynchronizations. A reference Ag/AgCl electrode was placed on the right and left mastoid processes. The skin under the reference electrodes was abraded with a pumice solution and thoroughly cleaned with isopropyl alcohol. The sampling rate was of 500 Hz.

EMG

A Biopac MP35 with Ag/AgCl bipolar configuration electrodes was used to monitor muscle activities. Electrodes were placed over the motor points of the left and right solei and tibiales anterior to monitor ankle flexion and extension. Electrode placement followed the SENIAM guidelines. The electrode placement sites were prepared by shaving the hairs and abrading the skin with an exfoliant cream. The area was then cleaned with isopropyl alcohol. Electrode centers were placed 30 mm away from each other along the muscle length and secured in place with tape. A reference electrode was placed on the lateral malleolus of the right foot. The sampling rate was 1 kHz. Data were down sampled to 500 Hz for analyses.

Virtual Reality Environment Eye Tracking and Reaction Time

An HTC VIVE virtual reality headset with integrated Tobii Pro infrared eye-tracking system was used to track focal vision during VR simulations. The HTC Vive headset has a binocular screen configuration that delivers optical flow based on pre-built VR environments. The Tobii Pro eye-tracking system is composed of two infrared cameras, one for each eye, and two circular arrays of infrared light dots. The infrared light is reflected by the retina and captured by the cameras, providing positioning of the eyes. A dynamic paradigm was delivered in the VR environment (Figure 4.4) in which participants were moving straight ahead in a procedurally generated tunnel. Every 5 seconds a ball-shaped target would appear in a random spot 15 meters away from the participant. The targets were stripped black and white, with ether a left or right tilt. Participants were instructed to pull the trigger on the controller when the target had a right tilt. Each target remained visible for 1.5 seconds and had a coded 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. Eye movement data were sampled at 120 Hz. A saccade was be defined as movement greater than 0.1°, within a maximum time limit of 15-150 ms, with an angular velocity greater than 20 °/s, and angular acceleration greater than 400 °/s, with a momentary fixation at the end of the movement[123]. Saccadic accuracy was determined by averaging the scores during the first 25 ms after initiation of the saccade. 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 2.4. *Virtual Reality Simulation Environment with Right-tilting Cue*

Testing Procedures

Participants were walked through and signed an informed consent when they arrived at the lab. Next, they completed a survey addressing their concussion history (Appendix B.1), and weekly physical activity levels (Appendix B.2). They were then prepped with the EEG cap and EMG electrodes. Next, participants received visual and verbal instructions about the paradigm before being asked to stand at a relaxed position on a Bertec force plate (sampling rate = 960 Hz). A 5-point calibration was then performed in the VR environment and a set of mock targets was used to visually verify the calibration at the beginning of each trial. They completed three trials, each with a duration of 30 seconds. Data across all devices were time-locked with markers.

Statistical Analyses

Data were first visually inspected and analyzed descriptively. Normality was assessed by dividing the *Skewness* by the *S.E. of Skewness*, and the *Kurtosis* by the *S.E. of Kurtosis*. A critical value of $z = .01$ was used to test this hypothesis. Independent samples t tests were conducted to compare the levels of physical activity (vigorous, moderate, walking), balance metrics (COP displacement, approximate entropy), and virtual reality metrics between groups. A two-way ANOVA was conducted to analyze the effects of concussion history and brain region-muscle pair on mean coherence values in each frequency bin. The level of significance was of $\alpha = .05$.

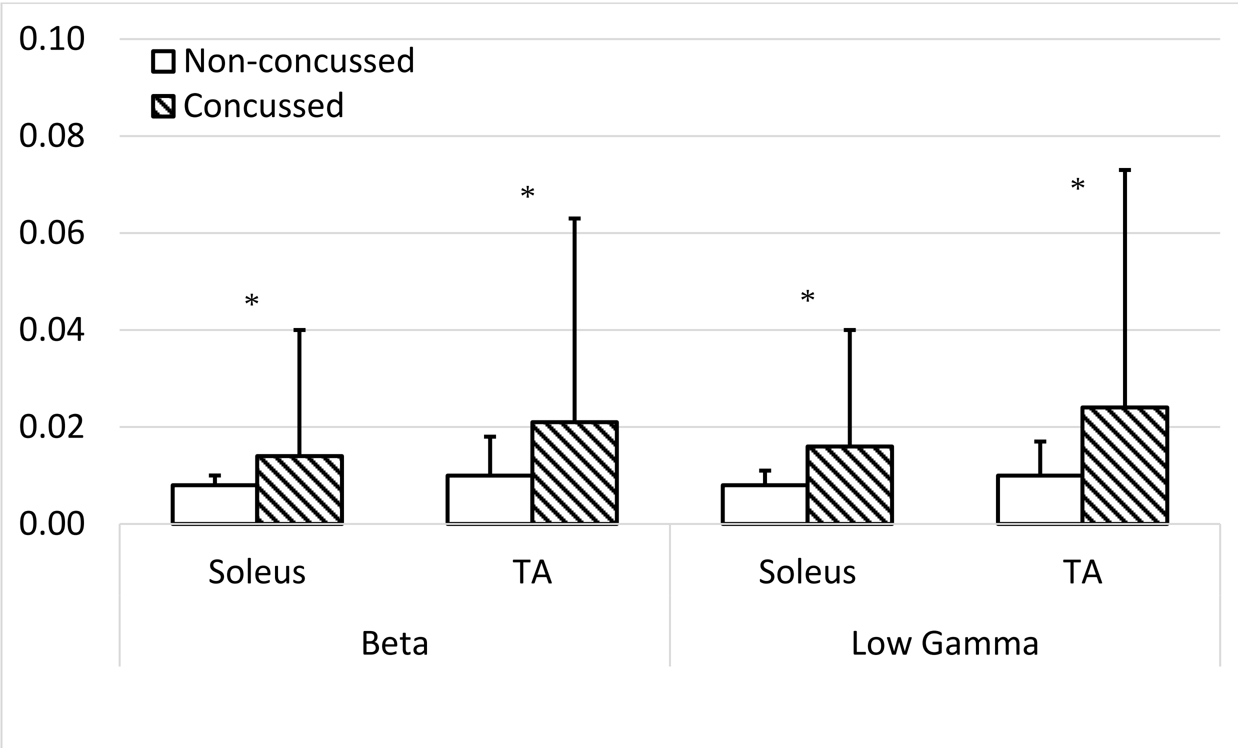
Data Reduction

Electroencephalographic data were re-referenced to average, bandpass filtered between 1-90 Hz, and epoched into segments of 15 seconds (1 trial). Electromyographic data were down-sampled to match the EEG sampling rate of 500 Hz and bandpass filtered between 1-250 Hz using a fourth order Butterworth zero-lag filter. Each trial was epoched to a length of 15 seconds, with the start time-locked to their corresponding epoched EEG trial. The magnitude-squared coherence was calculated for each individual trial pair of EEG-EMG data, with EEG data being averaged across four regions of the scalp, the left and right frontal cortex and sensorimotor strip. Cross-spectra of delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), low gamma (30-50 Hz), and high gamma (50-90 Hz) frequency bins were calculated for each individual trial, over each contralateral brain region, in relation to each one of the four leg muscles before being averaged across the three trials for each participant. The brain region-muscle pairs were as follows: right frontal cortex and left soleus (FC_R-S_L), right sensorimotor cortex and left soleus (SM_R-S_L), left frontal cortex and right soleus (FC_L-S_R), left sensorimotor cortex and the right soleus (SM_L-S_R), right frontal cortex and left tibialis anterior (FC_R-TA_L), right sensorimotor cortex and left tibialis anterior (SM_R-TA_L), left frontal cortex and right tibialis anterior (FC_L-TA_R), left sensorimotor cortex and the right tibialis anterior (SM_L-S_R),. Data were missing for one participant.

Results

A two-way ANOVA was conducted to analyze the effects of concussion history (non-concussed, concussed) and brain region-muscle pair (FC_R-S_L, SM_R-S_L, FC_L-S_R, SM_L-S_R, FC_R-TA_L, SM_R-TA_L, FC_L-TA_R, SM_L-S_R) DVs on mean coherence values in each frequency bin (delta, theta, alpha, beta, low gamma, high gamma) IV. For the solei muscles, there were significant main effects of concussion history on the beta, $F(1, 120) = 4.37$, $p = .039$, $\eta p = .035$, and low gamma, $F(1, 120) = 7.35$, $p = .008$, $\eta p = .058$, frequency bins. Similarly, for the tibiales anterior muscles, there were significant main effects of concussion history on the beta, $F(1, 120) = 4.49$, $p = .036$, $\eta p = .036$, and low gamma, $F(1, 120) = 6.12$, $p = .015$, $\eta p = .049$, frequency bins. In all cases, corticomuscular coherence in the beta and low gamma frequency bins increased in concussed participants when compared to their non-concussed counterparts. The results are summarized in Figure 4.5.

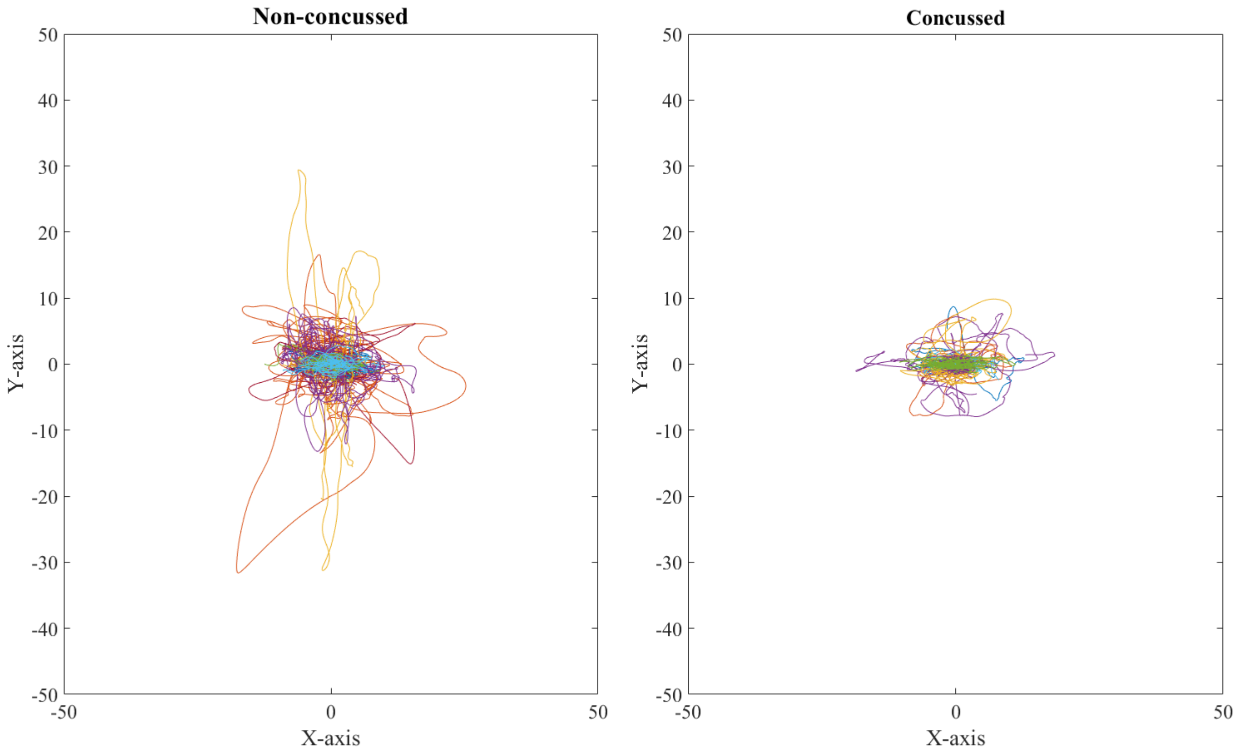
Figure 4.5. Means and standard deviations of corticomuscular coherence in beta and low gamma frequency bins for the solei and tibiales anterior muscles of concussed and non-concussed groups.



Note. TA: tibialis anterior; Beta = 12-30 Hz; Low-gamma = 30-50 Hz; *: statistically significant difference ($p < .05$) between concussed and non-concussed.

An independent samples t-test revealed statistically significant differences in anteroposterior COP displacement approximate entropy between non-concussed ($M = .02$, $SD = 0.05$) and concussed ($M = .10$, $SD = .12$) participants, $t(15.35) = -2.29$, $p = .036$, $d = .088$, as well as in mediolateral COP displacement approximate entropy between non-concussed ($M = .03$, $SD = .05$) and concussed ($M = .11$, $SD = .12$) participants, $t(15.00) = -2.33$, $p = .034$, $d = .090$. Levene's test of equality of variances was significant for both anteroposterior ($F = 33.31$, $p < .001$) and mediolateral ($F = 37.21$, $p < .001$) metrics. The effect sizes were small. A stabilogram with superimposed COP displacement traces for each participant is shown in Figure 4.6.

Figure 4.6. COP Displacement Traces for Non-concussed and Concussed Participants.



Note. X-axis: medio-lateral direction; Y-axis: antero-posterior direction; Displacements are in millimeters.

A series of independent samples t-tests were performed to investigate the difference in eye-tracking metrics between groups (non-concussed, concussed) after the cue was presented. The assumption of homogeneity of variance was met for all metrics. There were no differences between groups for time spent on target (lingering time), how close they spent to the center of the target (lingering time), how close to the actual center of the target they looked (score accuracy), and visual reaction time (visual RT). All metrics were calculated for the duration that the cue remained visible, except score accuracy, which was calculated for the first 25 ms after the presentation of the cue. The results are summarized in Table 4.2.

Table 4.2. Dynamic Virtual Reality Task Eye-Tracking Metrics Statistics

	Levene's		Independent Samples Student's t-test						
						Non-concussed		Concussed	
	F	*p*	*t*	*df*	*p*	*M*	*SD*	*M*	*SD*
Lingering Time	0.36	0.550	0.40	30	0.690	64.48	52.29	55.91	68.09
Mean Score	2.26	0.143	-0.65	30	0.519	7.75	1.23	8.00	7.95
Score Accuracy	1.66	0.207	-0.23	30	0.814	7.10	1.23	7.20	1.03
Visual RT	0.22	0.636	-1.02	21	0.318	0.17	0.09	0.21	0.08

Note. M = mean; SD = standard deviation; Levene's = Levene's test for equality of variances.

Discussion

In this project, we sought to investigate long-lasting oculomotor and postural control impairments in mTBI participants compared to non-concussed controls over the course of 8 years post-trauma. We initially hypothesized that some level of oculomotor and balance impairments would be observed in concussed participants several months after their head trauma incident. We also expected to find disparaging neural modulation between groups. The participants in both groups had similar levels of weekly physical activity. Both concussed and non-concussed groups performed approximately two hours and forty-five minutes of vigorous activity and approximately one hour of walking activity per week. The concussed group, on average, had an approximately 88% higher volume of moderate activity than the non-concussed group, but the variability in the concussed group was also large, which did not afford a statistically significant difference.

Our analyses of oculomotor control metrics revealed no differences between groups in terms of the variables chosen for this project. Our findings contradict typical results in eye-tracking concussion trials[124,125], but it is worth noting that these studies have tested mTBI patients withing

72 hours[124] and 14 days[125] from the time they had suffered the concussion. One of the possibilities for our findings is that the impairments commonly observed subside over time as neuromuscular control adapts. Another possibility is the difference in methodologies employed in this study, i.e., performing eye-tracking tasks while standing instead of sitting down. We have previously demonstrated that VR simulations and blinding (eyes closed) can produce significant changes in postural control when used to induce balance perturbations[30]. Nevertheless, it remained unclear if oculomotor control would also be affected during a balance task if attentional focus was directed towards the visual task. This was an important question in this project, as the VR visual secondary cognitive task served not only as an eye-tracking paradigm, but also as an optical flow-induced balance perturbation paradigm.

The analysis of COP trajectories and overall displacement revealed a stark difference between non-concussed and concussed participants, with COP displacement being greater in the non-concussed group while approximate entropy was greater in the concussed group. Previous findings in a cohort of athletes that had suffered concussions suggest that sway metrics (e.g., COP displacement) would normalize after three weeks while non-linear dynamics could detect differences between concussed and non-concussed participants up until 90 days post-concussion[57]. In contrast to their findings, we observed reduced postural sway in the concussed group and increased non-linear dynamics (approximate entropy) in the concussed group. That is to suggest that concussed participants had shorter and more variable sway patterns while non-concussed participants had greater and more uniform sway patterns. Our findings are in line with those of Cavanaugh, Mercer & Stergiou (2007), who demonstrated that postural sway approximate entropy increases when participants are engaged in a secondary cognitive task[126]. Furthermore, increased complexity in COP trajectories may be the outcome of employing cognitive resources to actively control posture by increasing degrees of freedom and attenuation of movement[127]. The overall result are shorter COP displacements and COP velocity, leading to increased perceived stability.

The corticomuscular coherence values supported by our balance metrics. There were no statistically significant differences between left and right-side brain-muscle couples. There were also no differences in coherence measurements between the frontal and sensorimotor cortexes. These findings suggest that neural modulations and muscle activity couplings were independent of limb dominance, and that the differences observed in the cerebral cortex between groups were similar across the frontal and sensorimotor cortexes. Overall, participants with a history of concussion had greater beta and low gamma corticomuscular coherence in the solei and tibiales anterior muscles, which suggests that increased processing demands observed in a concussive state are also present in lower-extremity muscle activations. There is evidence that beta and low gamma desynchronization is decreased during the first 12 months after a concussive event[23]. Conversely, Dunkley et al. (2018) described increased beta and low gamma activity in the motor cortex and frontal cortex within three months of injury[128]. Our results imply that those intra-cortical modulations are being passed on to peripheral muscle control, which would explain, at least in part, the observed impairment and increased variability of postural control in concussed participants. Lastly, the increased coherence in the beta and low gamma frequency bins in the frontal cortex and sensorimotor cortex suggest a link between the increased processing demands, both cognitive and sensorimotor, when concussed participants are submitted to a cognitive task.

Perhaps, concussion-related impairments of cognitive processing and postural control are not necessarily impairments, but a shift in specific strategy to circumvent cortical structure damage. It is well-known that EMG amplitude increases with activation intensity[129] and that increased activation amplitude during dynamic loading is a product of faster cross-bridge cycling[130]. Similarly, cortical activity shifts towards greater frequencies (e.g., from beta to low gamma) during dynamic force tasks, especially when rapid integration of somatosensory and visual information is present[105]. By establishing a link between beta and low-gamma bands between lower leg muscles, their contralateral loci of neural control, and the corresponding cognitive processing area we have now tied together these two phenomena. This link had previously been established at lower frequencies in non-concussed individials[131], but it remained unclear if the increased cortical activity in higher frequency bins, due to concussion, would also be reflected in muscle activations. Considering that higher frequencies observed in muscle activations during dynamic loading appear to be independent of contraction velocity and power output[132], instead being more closely related to the type of muscle fiber being recruited[133], the conservative postural control strategies adopted by concussed individuals[134] may persist far past early recovery. If so, the road to recovery may need to be based on learning new strategies instead of regaining lost ones, i.e., training.

This project is not without limitations. The biggest one is, perhaps, the absence of a greater, and more uniformly distributed concussed cohort in terms of time since their sustained brain trauma. Secondly, the VR environment deployed with the eye-tracking paradigm was novel, which makes comparisons in the literature difficult, if not currently impossible. The metrics chosen for the assessment of oculomotor function may also not be the most sensitive, and thus serve as modest guidance for future research projects. Such projects should also consider segregating each group into subgroups, according to their levels of physical activity.

To conclude, we managed to demonstrate that concussion-related balance impairments not only persist through the years, but there is also a link between cortical and lower extremity muscle activity dysfunction. Future endeavors should focus on either a more uniform or a more concise timing in concussion history, as well as some different metrics of oculomotor function.

Acknowledgements

This project was supported by the Kinesiology Department at East Carolina University, and by the Matching Dissertation Grant from the International Society of Biomechanics.

Chapter 5: Discussion

In this manuscript we have described how traumatic brain injuries are a major health concern in the US[1] and delineated how they result in long-lasting neurological impairment[3], sometimes permanent[4], which can translate into lower extremity and ocular motor control impairment[5]. We have also discussed how current methods of recovery assessment can be inaccurate during the acute phase[7,8], and may fail to identify impairments after usual symptoms subside during early recovery[5]. These methods are also indirect and not accurate at detecting underlying motor issues[12,13]. In the absence of specific neuromuscular markers, the ability and the reliability of diagnostics is compromised. In an attempt to address this issue, we sought to discover and discretely define potential biological markers associated with it. Our specific aims were to develop a virtual reality environment in which we could implement known eye-tracking methodologies and validate its accuracy in differentiating between non-concussed and concussed cohorts (Chapter 2), investigate the presence of neural signatures that could differentiate between a concussive state and a fatigue state (Chapter 3), and determine if long-lasting oculomotor and peripheral muscle control impairments could be reliably detected in a concussed cohort several years post-trauma, as well as if there was a link between those impairments and a higher incidence of lower body injurie rates post-trauma when compared to non-concussed controls (Chapter 4).

Virtual reality and eye-tracking as means of concussion testing are still a relatively new field which seeks not only to implement new testing methodologies based on the freedom afforded by the VR environment, but also to recreate reliable laboratorial methods in the VR environment, with the purpose of creating immersion and eliminating outside distractors[30]. It is not without limitations, but overall, eye tracking in VR appears to produce similar responses to eye-tracking in a real world setting as far as vergence and focal distance are concerned[135]. Our approach took advantage of previous work[31] to determine cue size, and eye movements of interest: circular smooth pursuit, vertical/horizontal smooth pursuit, and vertical/horizontal saccades. Within those conditions, we analyzed eye movements for each individual eye. The metrics chosen for the analyses were linear and non-linear. Linear metrics were tracking error, root mean squared tracking error, and angular tracking error, while the non-linear metrics were standard deviation of mean squared tracking error and sample entropy of tracking error. The pool of concussed participants was heterogenous in terms of how long after a concussion they were tested, which may have affected the results. Nevertheless, we have found that non-linear measurements of saccadic movements were the most sensitive to oculomotor impairments, even many years post-trauma. More specifically, the standard deviation of mean squared tracking error of horizontal saccades, which had a moderate effect size (d = .469). Since the focus of this first aim was methodological. As such, its report includes detailed descriptions of the environment and of the mathematical equations used, including the VR googles used (HTC Vive Pro) and the eye trackers (Tobii Pro VR).

Our next aim (Chapter 3) was to determine if it was possible to reliably differentiate between impairments caused by a concussive state and physical exertion, a common condition for athletes and warfighters. To achieve that aim, a cohort of recently concussed (recovering from mTBI) young adult participants was tested alongside non-concussed controls. Groups were comprised of a mix of ROTC cadets, collegiate athletes, and law enforcement officers. A mix of cortical activity (EEG) and balance metrics were assessed while participants were submitted to different balance-challenging conditions: eyes open, eyes closed, standing on their dominant leg, performing a mental task (counting down from a random number in intervals of seven), a virtual reality baseline in which the lab space was recreated in VR, and a VR optical flow induced balance perturbation in which an anteroposterior sway of the room was introduced[30]. Non-concussed participants underwent a fatigue-inducing protocol which consisted of a 30-min walk[66] carrying a backpack weighing 27 kg at pace in which they could maintain a somewhat hard-to-hard level of physical activity as measured by heart rate and rate of perceived exertion. Our results showed a 27.3% overall increase in whole brain spectral power in the non-concussed group after they were submitted to the fatigue protocol. When the concussed and non-concussed post-fatigue groups were compared, a stark difference was observed in the alpha and theta frequency bands between groups, along with a decrease in overall spectral power in the motor cortex and central sulcus of concussed participants. More specifically, concussed participants had overall lower alpha and theta power than non-concussed fatigued participants, but while theta increased in the non-concussed group, it decreased in the concussed group.

Alpha and theta rhythms are closely linked to cognitive resources[76,77], with increases in alpha and theta power being observed when cognitive resources are exhausted[78,79], which is in agreement with our findings for the fatigued group. This was evidence that a relatively short bout of physical activity is sufficient to exhaust cognitive resources, which may in turn affect sensory intake and processing[136]. Theta power increases are also linked to increased cognitive demands, when an individual must exert cognitive control over a task[81]. This supports our belief that this protocol was sufficient to disrupt their neurocognitive processing. In the concussed group, it was reasonable that their alpha and theta activity were depressed, as this has been previously observed and linked to increasing demands for active processing in the cortex[83,84]. Moreover, the alpha-theta ratio is associated with the modulation of blood flow in the cerebral cortex; increases in alpha spectral power are inversely related levels of blood blow and theta spectral power is directly related to it[86]. It is no surprise that we have observed increased alpha and decreased theta spectral power in concussed participants, evidence of overall reduced blood flow in the cortex, while the opposite was observed in the non-concussed group shortly after the induced fatigue state. This shift in the alpha-theta ratio was previously reported by peers[92,93].

Finally, differences between groups were also observed in postural control. Concussed participants had greater anteroposterior COP velocity and approximate entropy, with decreased COP displacement when submitted to the sinusoidal VR balance perturbation. When compared to the non-concussed group, linear balance metrics either remained unchanged or increased after the fatiguing protocol, while non-linear metrics decreased. Specifically, there were decreases in complexity during the fatigue state while the concussed group showed greater complexity when compared to either the pre- or post-fatigue non-concussed group. This supported our initial hypothesis that the VR induced optical flow postural control perturbation would be successful in challenging the participants' balance in ways that would elicit a disparaging response between a non-concussed fatigue state and a concussed state. Concussed participants also showed much greater variation in balance metrics when performing the cognitive task. This outcome was further supported by our cortical spectral power analyses, where we observed higher cognitive demands in the concussed group.

Our third aim (Chapter 4) sought to expand on these previous findings by introducing a novel VR optical flow protocol, which served a double purpose as an eye-tracking paradigm and as a secondary cognitive task to challenge the balance of non-concussed controls and concussed participants that were past their recovery period, up until 8 years post-trauma. The objectives of this aim were to assess if the new optical flow paradigm, along with the different metrics selected, could elicit similar balance perturbations in participants with a history of concussion, and to investigate if these different metrics would be sensitive enough to detect oculomotor impairments in support of a standalone testing using solely eye-tracking in a VR environment. Concomitantly, we also sought to determine if the impairments observed would be associated with evidence of impairments in corticomuscular coupling.

To achieve our objective, we implemented a novel VR environment in which participants had to discriminate between randomly appearing cues while standing on a force platform. At the same time, we measured their cortical activity and lower extremity muscle activity. Visual metrics chosen were the time spent looking at the cue, how close to the center of the cue participants focused on, how close to the center of the cue they got during their initial saccadic movement, and their visual reaction time. Balance metrics chosen were COP displacement and complexity (approximate entropy). Corticomuscular coherence was calculated between the contralateral sensorimotor and frontal cortexes and the respective soleus and tibialis anterior muscles. Levels of weekly physical activity were used to match the groups.

The groups displayed similar levels of physical activity. There was substantial variance in the levels of moderate physical activity in the concussed group, which may have been exacerbated by a lack of a more homogenous cohort in terms of time since their concussive event. Oculomotor metrics were also unsuccessful in detecting differences between groups. While they are typically sensitive during the early stages of concussion recovery[124,125], we hypothesize that it is possible that concussed participants adapted around those impairments over time, to the point of being able to eventually exhibit typical oculomotor control levels. Our protocol also differed from commonly used eye tracking paradigms by having participants stand and perform a visual identification and choice reaction task. We believe the task took precedence in the higher processes of concussed participants and served solely as a challenge to postural control.

This assumption was supported by the balance metrics, but clearly differed from participants recovering from concussion. Non-concussed participants exhibited typical COP trajectories in both mediolateral and anteroposterior directions, while these same trajectories were substantially shortened in the concussed cohort. Conversely, non-concussed participants had lower variability (approximate entropy) in their COP trajectories, while the concussed group had grater variability in their COP trajectories. This finding points to the possibility of a different long-term adaptation post-concussive trauma, given that opposing results were observed in the group that was undergoing concussion recovery (see Chapter 3). There are evidence to support the sensitivity of approximate entropy as a reliable measurement of postural control impairment following a concussion[57], especially while they are engaged in a secondary cognitive task[126].

Corticomuscular coherence results were supportive of our findings about balance control. There were significant differences between groups in terms of beta and low gamma correlations in connections between the frontal cortex and sensorimotor cortex with the lower extremity muscles, solei and tibiales anterior. Coherence over those frequency bins was increased in the concussed group, suggesting that the increased excitability and cognitive demands stemming from a concussive injury overspill to their muscle control. This may have caused shorter and jerkier COP traces. Furthermore, it was surprising to not find any coherence differences in the theta and alpha frequency bands, which were the primary neurological markers to differentiate concussed from non-concussed participants in our second aim (see Chapter 3). It is unclear, at this point, if the introduction of a visual cognitive task caused a shift in the processing demands, depressing theta and alpha, which we propose should be the focus of future research. However, we cannot discard the main difference between the two concussed groups: time post-trauma. A fair assumption here would be that, over time, significant neural reorganization occurs, as evidenced by changes in postural control. Alternatively, it is possible that the beta and gamma couplings observed were due solely to the introduction of a visual task that promotes dynamic force output[105].

Our findings are overall satisfactory to the initial proposed investigation. Even so, we managed to detect corticomuscular coherence and postural control differences capable of differentiating between non-concussed and long-term post-trauma concussed participants. We were also able to establish a link between the observed changes in corticomuscular coherence and postural control adaptations observed in the concussed group. The virtual reality protocol used needs further testing and development if it is to serve as a standalone assessment tool for long-term motor control symptoms of concussion.

In summary, virtual reality proved to be a valuable tool in detecting concussion-derived impairments of oculomotor function, and to deliver optical flow-induced postural control-challenging perturbations, making possible the detection of balance impairments several months past concussion. It can also be used to elicit significant cortical manifestations that allow the distinction between two disparate groups. The assessment of balance metrics continues to be a valuable tool in the determination of concussion impairment, but we have expanded its capability by detecting differences between groups, supported by electroencephalographic data, several months post-trauma. We also managed to identify, in the alpha-theta ratio, a clear neurological marker that can differentiate between those that are recovering from a concussion and those that are not concussed but are under some level of fatigue stemming from a somewhat hard-to-hard bout of physical exertion. When expanded into a long-term analysis, EEG results suggested that although cognitive processing is depressed during early concussion recovery, it is substantially more demanding several months after a concussive event. Finally, we established a link between increased frequency rates, e.g., neural demands, in the cerebral cortex, in the cognitive and sensorimotor processing areas, and the leg muscles, which could be responsible for atypical modifications of balance control in the long-term post-trauma.

These findings are a substantial contribution to the literature, with the potential to change how we address concussion recovery. Specifically, it poses the question whether the neurological trauma is in fact permanent. If so, it remains to be determined if people adapt their neurological pathways and motor control strategies to circumvent those impairments, assuming structural plasticity is possible after major damage to the structural pathways[137].

Limitations

Our third aim (Chapter 4) could certainly benefit from a higher pool of participants, and more uniformly distributed concussed cohort in terms of time since their sustained brain trauma. Secondly, the VR environment deployed with the eye-tracking paradigm was novel, which makes comparisons in the literature difficult, if not currently impossible. The metrics chosen for the assessment of oculomotor function may also not be the most sensitive, and thus serve as modest guidance for future research projects.

Future Directions

Future research endeavors should consider accounting for the presence of control-drive stiffening of the target postural control muscles. Activations of fast-twitch fibers are expected to reduce stiffening by not allowing slow-twitch fibers enough time to activate fully[133]. However, elderly populations and those that had previously experienced falls[138] typically employ stiffening strategies in attempts to prevent their COP from moving beyond their base of support[139] while also exhibiting greater activation of faster muscle fibers[140]. Furthermore, greater focus should be given to the exploration of non-linear balance and oculomotor control metrics. Lastly, all three aims would benefit greatly from substantial data gathering efforts to address the lack of comparable projects in the body of knowledge.

REFERENCES

1. of Health D, Services H, for Disease Control C. Centers for Disease Control and Prevention Prevention and Control SURVEILLANCE REPORT Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths TBI: SURVEILLANCE REPORT ACKNOWLEDGEMENTS. Published online 2014. Accessed September 9, 2019. www.cdc.gov/TraumaticBrainInjury

2. Daneshvar DH, Nowinski CJ, McKee AC, Cantu RC. The Epidemiology of Sport-Related Concussion. Clin Sports Med. 2011;30(1):1-17. doi:10.1016/j.csm.2010.08.006

3. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus Statement on Concussion in Sport: The 4th International Conference on Concussion in Sport, Zurich, November 2012. J Athl Train. 2013;48(4):554-575. doi:10.4085/1062-6050-48.4.05

4. Giza CC, Hovda DA. The New Neurometabolic Cascade of Concussion. Neurosurgery. 2014;75:S24-S33. doi:10.1227/NEU.0000000000000505

5. Rutherford WH, Merrett JD, McDonald JR. Symptoms at one year following concussion from minor head injuries. Injury. 1979;10(3):225-230. doi:10.1016/0020-1383(79)90015-9

6. Labutta RJ. Medical Aspects of Traumatic Brain Injury (TBI). In: Presentation at the Workshop on Harnessing Operational Systems Engineering to Improve Traumatic Brain Injury Care in the Military Health System. National Academies; 2008.

7. Valovich McLeod TC, Bay RC, Heil J, McVeigh SD. Identification of Sport and Recreational Activity Concussion History Through the Preparticipation Screening and a Symptom Survey in Young Athletes. Clin J Sport Med. 2008;18(3):235-240. doi:10.1097/JSM.0b013e3181705756

8. Taghdiri F, Varriano B, Tartaglia MC. Assessment of Oculomotor Function in Patients With Postconcussion Syndrome. J Head Trauma Rehabil. 2017;32(5):E55-E67. doi:10.1097/HTR.0000000000000286

9. Kenzie ES, Parks EL, Bigler ED, Lim MM, Chesnutt JC, Wakeland W. Concussion As a Multi-Scale Complex System: An Interdisciplinary Synthesis of Current Knowledge. Front Neurol. 2017;8:513. doi:10.3389/fneur.2017.00513

10. America BIA of. Diagnosing brain injury. Accessed November 6, 2019. https://www.biausa.org/brain-injury/about-brain-injury/diagnosis

11. Rose SC, Fischer AN, Heyer GL. How long is too long? The lack of consensus regarding the post-concussion syndrome diagnosis. Brain Inj. 2015;29(7-8):798-803. doi:10.3109/02699052.2015.1004756

12. WHO. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. 1st ed. World Health Organization; 1992. Accessed March 22, 2019. https://www.who.int/classifications/icd/en/bluebook.pdf?ua=1

13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596

14. Kardouni JR, Shing TL, McKinnon CJ, Scofield DE, Proctor SP. Risk for Lower Extremity Injury After Concussion: A Matched Cohort Study in Soldiers. J Orthop Sport Phys Ther. 2018;48(7):533-540. doi:10.2519/jospt.2018.8053

15. Olejniczak P. Neurophysiologic basis of EEG. In: Journal of Clinical Neurophysiology. Vol 23. ; 2006:186-189. doi:10.1097/01.wnp.0000220079.61973.6c

16. Ruiz-Gómez SJ, Hornero R, Poza J, Maturana-Candelas A, Pinto N, Gómez C. Computational modeling of the effects of EEG volume conduction on functional connectivity metrics. Application to Alzheimer's disease continuum. J Neural Eng. 2019;16(6):066019. doi:10.1088/1741-2552/ab4024

17. Mannix R, Berglass J, Berkner J, et al. Chronic gliosis and behavioral deficits in mice following repetitive mild traumatic brain injury. J Neurosurg. 2014;121(6):1342-1350. doi:10.3171/2014.7.JNS14272

18. Ojo JO, Mouzon B, Algamal M, et al. Chronic repetitive mild traumatic brain injury results in reduced cerebral blood flow, axonal injury, gliosis, and increased T-tau and tau oligomers. J Neuropathol Exp Neurol. 2016;75(7):636-655. doi:10.1093/jnen/nlw035

19. Koenig T, Marti-Lopez F, Valdes-Sosa P. Topographic Time-Frequency Decomposition of the EEG. Neuroimage. 2001;14(2):383-390. doi:10.1006/nimg.2001.0825

20. Hirsch LJ, Brenner RP, Drislane FW, et al. The ACNS Subcommittee on Research Terminology for Continuous EEG Monitoring: Proposed Standardized Terminology for Rhythmic and Periodic EEG Patterns Encountered in Critically Ill Patients. J Clin Neurophysiol. 2005;22(2):128-135. doi:10.1097/01.WNP.0000158701.89576.4C

21. Srinivasan R, Nunez PL, Silberstein RB. Spatial filtering and neocortical dynamics: estimates of EEG coherence. IEEE Trans Biomed Eng. 1998;45(7):814-826. doi:10.1109/10.686789

22. Thompson J, Sebastianelli W, Slobounov S. EEG and postural correlates of mild traumatic brain injury in athletes. Neurosci Lett. 2005;377(3):158-163. doi:10.1016/j.neulet.2004.11.090

23. Munia TTK, Gendreau JL, Verma AK, et al. Preliminary results of residual deficits observed in athletes with concussion history: Combined EEG and cognitive study. In: 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). Vol 2016-Octob. IEEE; 2016:41-44. doi:10.1109/EMBC.2016.7590635

24. Teel EF, Ray WJ, Geronimo AM, Slobounov SM. Residual alterations of brain electrical activity in clinically asymptomatic concussed individuals: An EEG study. Clin Neurophysiol. 2014;125(4):703-707. doi:10.1016/j.clinph.2013.08.027

25. Cao C, Slobounov S. Alteration of cortical functional connectivity as a result of traumatic brain injury revealed by graph theory, ICA, and sLORETA analyses of EEG signals. IEEE Trans Neural Syst Rehabil Eng. 2010;18(1):11-19. doi:10.1109/TNSRE.2009.2027704

26. Virji-Babul N, Hilderman CGE, Makan N, et al. Changes in functional brain networks following sports-related concussion in adolescents. J Neurotrauma. 2014;31(23):1914-1919. doi:10.1089/neu.2014.3450

27. Conley AC, Cooper PS, Karayanidis F, et al. Resting State Electroencephalography and Sports-Related Concussion: A Systematic Review. J Neurotrauma. 2019;36(1):1-13. doi:10.1089/neu.2018.5761

28. Kaltiainen H, Helle L, Liljeström M, Renvall H, Forss N. Theta-Band Oscillations as an Indicator of Mild Traumatic Brain Injury. Brain Topogr. 2018;31(6):1037-1046. doi:10.1007/s10548-018-0667-2

29. Lewine JD, Plis S, Ulloa A, et al. Quantitative EEG Biomarkers for Mild Traumatic Brain Injury. J Clin Neurophysiol. 2019;36(4):298-305. doi:10.1097/WNP.0000000000000588

30. Sandri Heidner G, Rider PM, Mizelle JC, O'Connell CM, Murray NP, Domire ZJ. Anterior-posterior balance perturbation protocol using lifelike virtual reality environment. J Appl Biomech. 2020;36(4):244-248. doi:10.1123/JAB.2019-0130

31. Hunfalvay M, Murray NP, Mani R, Carrick FR. Smooth Pursuit Eye Movements as a Biomarker for Mild Concussion within 7-Days of Injury. https://doi.org/101080/0269905220212012825. 2021;35(14):1682-1689. doi:10.1080/02699052.2021.2012825

32. Hudson S, Matson-Barkat S, Pallamin N, Jegou G. With or without you? Interaction and immersion in a virtual reality experience. J Bus Res. 2019;100:459-468. doi:10.1016/J.JBUSRES.2018.10.062

33. Combs PR, Ford CB, Campbell KR, Carneiro KA, Mihalik JP. Influence of Self-reported Fatigue and Sex on Baseline Concussion Assessment Scores. Orthop J Sport Med. 2019;7(1):2325967118817515. doi:10.1177/2325967118817515

34. Lindsey J, Cheever K, Mansell JL, Phillips J, Tierney RT. Effect of Fatigue on Ocular Motor Assessments. Athl Train Sport Heal Care. 2017;9(4):177-183. doi:10.3928/19425864-20170420-03

35. Cifu DX, Wares JR, Hoke KW, Wetzel PA, Gitchel G, Carne W. Differential Eye Movements in Mild Traumatic Brain Injury Versus Normal Controls. J Head Trauma Rehabil. 2015;30(1):21-28. doi:10.1097/HTR.0000000000000036

36. Heitger MH, Jones RD, Macleod AD, Snell DL, Frampton CM, Anderson TJ. Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. Brain. 2009;132(10):2850-2870. doi:10.1093/brain/awp181

37. Orban De Xivry JJ, Lefèvre P. Saccades and pursuit: two outcomes of a single sensorimotor process. J Physiol. 2007;584(Pt 1):11. doi:10.1113/JPHYSIOL.2007.139881

38. Purves D, Augustine GJ, Fitzpatrick D, et al. Neuroscience. 2nd ed. Sinauer Associates; 2001.

39. Stubbs JL, Corrow SL, Kiang B, Panenka WJ, Barton JJS. The effects of enhanced attention and working memory on smooth pursuit eye movement. Exp Brain Res. 2018;236(2):485-495. doi:10.1007/s00221-017-5146-6

40. Maruta J, Spielman LA, Rajashekar U, Ghajar J. Visual Tracking in Development and Aging. Front Neurol. 2017;8:640. doi:10.3389/fneur.2017.00640

41. Liversedge SP, Findlay JM. Saccadic eye movements and cognition. Trends Cogn Sci. 2000;4(1):6-14. doi:10.1016/S1364-6613(99)01418-7

42. Hoffman JE, Subramaniam B. The role of visual attention in saccadic eye movements. Percept Psychophys. 1995;57(6):787-795. doi:10.3758/BF03206794

43. Wright WG, Tierney RT, McDevitt J. Visual-vestibular processing deficits in mild traumatic brain injury. J Vestib Res Equilib Orientat. 2017;27(1):27-37. doi:10.3233/VES-170607

44. Robitaille N, Jackson PL, Hébert LJ, et al. A Virtual Reality avatar interaction (VRai) platform to assess residual executive dysfunction in active military personnel with previous mild traumatic brain injury: proof of concept. Disabil Rehabil Assist Technol. 2017;12(7):758-764. doi:10.1080/17483107.2016.1229048

45. Wright WG, McDevitt J, Tierney R, Haran FJ, Appiah-Kubi KO, Dumont A. Assessing subacute mild traumatic brain injury with a portable virtual reality balance device. Disabil Rehabil. 2017;39(15):1564-1572. doi:10.1080/09638288.2016.1226432

46. Lake DE, Richman JS, Pamela Griffin M, Randall Moorman J. Sample entropy analysis of neonatal heart rate variability. Am J Physiol - Regul Integr Comp Physiol. 2002;283(3 52-3):789-797. doi:10.1152/ajpregu.00069.2002

47. Sussman ES, Ho AL, Pendharkar A V., Ghajar J. Clinical evaluation of concussion: The evolving role of oculomotor assessments. Neurosurg Focus. 2016;40(4):E7. doi:10.3171/2016.1.FOCUS15610

48. Saigal R, Berger MS. The long-term effects of repetitive mild head injuries in sports. Neurosurgery. 2014;75:S149-S155. doi:10.1227/NEU.0000000000000497

49. Kontos AP, Deitrick JMA, Collins MW, Mucha A. Review of vestibular and oculomotor screening and concussion rehabilitation. J Athl Train. 2017;52(3):256-261. doi:10.4085/1062-6050-51.11.05

50. Murray NG, Ambati VNP, Contreras MM, Salvatore AP, Reed-Jones RJ. Assessment of oculomotor control and balance post-concussion: A preliminary study for a novel approach to concussion management. Brain Inj. 2014;28(4):496-503. doi:10.3109/02699052.2014.887144

51. Kelly KM, Kiderman A, Akhavan S, et al. Oculomotor, Vestibular, and Reaction Time Effects of Sports-Related Concussion: Video-Oculography in Assessing Sports-Related Concussion. J Head Trauma Rehabil. 2019;34(3):176-188. doi:10.1097/HTR.0000000000000437

52. Elbaum T, Wagner M, Botzer A. Cyclopean vs. Dominant Eye in Gaze-Interface-Tracking. J Eye Mov Res. 2017;10(1). doi:10.16910/JEMR.10.1.2

53. Popelka S, Brychtova A. Eye-tracking Study on Different Perception of 2D and 3D Terrain Visualisation. http://dx.doi.org/101179/1743277413Y0000000058. 2013;50(3):240-246. doi:10.1179/1743277413Y.0000000058

54. Dan A, Reiner M. EEG-based cognitive load of processing events in 3D virtual worlds is lower than processing events in 2D displays. Int J Psychophysiol. 2017;122:75-84. doi:10.1016/J.IJPSYCHO.2016.08.013

55. Yaggie J, Armstrong WJ. Effects of Lower Extremity Fatigue on Indices of Balance. J Sport Rehabil. 2004;13(4):312-322. doi:10.1123/JSR.13.4.312

56. Simoneau M, Bégin F, Teasdale N. The effects of moderate fatigue on dynamic balance control and attentional demands. J Neuroeng Rehabil. 2006;3(1):1-9. doi:10.1186/1743-0003-3-22/FIGURES/4

57. Purkayastha S, Adair H, Woodruff A, et al. Balance Testing Following Concussion: Postural Sway versus Complexity Index. PM&R. 2019;11(11):1184-1192. doi:10.1002/PMRJ.12129

58. Millet GY. Can Neuromuscular Fatigue Explain Running Strategies and Performance in Ultra-Marathons? Sport Med. 2011;41(6):489-506. doi:10.2165/11588760-000000000-00000

59. Paillard T. Effects of general and local fatigue on postural control: A review. Neurosci Biobehav Rev. 2012;36(1):162-176. doi:10.1016/j.neubiorev.2011.05.009

60. Vuillerme N, Hintzy F. Effects of a 200 W–15 min cycling exercise on postural control during quiet standing in healthy young adults. Eur J Appl Physiol. 2007;100(2):169-175. doi:10.1007/s00421-007-0419-6

61. Horlings CGC, Carpenter MG, Küng UM, Honegger F, Wiederhold B, Allum JHJ. Influence of virtual reality on postural stability during movements of quiet stance. Neurosci Lett. 2009;451(3):227-231. doi:10.1016/j.neulet.2008.12.057

62. Chiarovano E, de Waele C, MacDougall HG, Rogers SJ, Burgess AM, Curthoys IS. Maintaining Balance when Looking at a Virtual Reality Three-Dimensional Display of a Field of Moving Dots or at a Virtual Reality Scene. Front Neurol. 2015;6:164. doi:10.3389/fneur.2015.00164

63. Bideau B, Kulpa R, Ménardais S, et al. Real Handball Goalkeeper vs. Virtual Handball Thrower. Presence. 2003;12(4):411-421. doi:10.1162/105474603322391631

64. McDevitt J, Appiah-Kubi KO, Tierney R, Wright WG. Vestibular and Oculomotor Assessments May Increase Accuracy of Subacute Concussion Assessment. Int J Sports Med. 2016;37(9):738-747. doi:10.1055/s-0042-100470

65. Broglio SP, Ferrara MS, Macciocchi SN, Baumgartner TA, Elliott R. Test-retest reliability of computerized concussion assessment programs. J Athl Train. 2007;42(4):509-514. doi:10.1016/S0162-0908(09)79464-4

66. Krajewski S. Energy cost of heavy load carriage and prolonged walking in ROTC collegiate participants. Published online 2014. Accessed March 22, 2019. http://thescholarship.ecu.edu/handle/10342/4418

67. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. Scand J Work Environ Heal. 1990;16(SUPPL. 1):55-58. doi:10.5271/sjweh.1815

68. Reed JL, Pipe AL. The talk test. Curr Opin Cardiol. 2014;29(5):475-480. doi:10.1097/HCO.0000000000000097

69. Doering TM, Reaburn PR, Borges NR, Cox GR, Jenkins DG. The Effect of Higher Than Recommended Protein Feedings Post-Exercise on Recovery Following Downhill Running in Masters Triathletes. Int J Sport Nutr Exerc Metab. 2017;27(1):76-82. doi:10.1123/ijsnem.2016-0079

70. Yaggie JA, McGregor SJ. Effects of isokinetic ankle fatigue on the maintenance of balance and postural limits. Arch Phys Med Rehabil. 2002;83(2):224-228. Accessed March 22, 2019. http://www.ncbi.nlm.nih.gov/pubmed/11833026

71. Bai OU, Nakamura M, Nagamine T, Ikeda A, Shibasaki H. Blink artifact elimination in electroencephalographic records based on discrete cosine transform domain modeling. Front Med Biol Eng. 2001;11(3):191-206. Accessed March 22, 2019. http://www.ncbi.nlm.nih.gov/pubmed/11898901

72. Bai O, Vorbach S, Hallett M, Floeter MK. Movement-related cortical potentials in primary lateral sclerosis. Ann Neurol. 2006;59(4):682-690. doi:10.1002/ana.20803

73. Slobounov S, Cao C, Sebastianelli W, Slobounov E, Newell K. Residual deficits from concussion as revealed by virtual time-to-contact measures of postural stability. Clin Neurophysiol. 2008;119(2):281-289. doi:10.1016/j.clinph.2007.10.006

74. Ghasemi A, Zahediasl S. Normality Tests for Statistical Analysis: A Guide for Non-Statisticians. Int J Endocrinol Metab. 2012;10(2):486. doi:10.5812/IJEM.3505

75. Mishra P, Pandey CM, Singh U, Gupta A, Sahu C, Keshri A. Descriptive Statistics and Normality Tests for Statistical Data. Ann Card Anaesth. 2019;22(1):67. doi:10.4103/ACA.ACA_157_18

76. Von Stein A, Sarnthein J. Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. Int J Psychophysiol. 2000;38(3):301-313. doi:10.1016/S0167-8760(00)00172-0

77. Ito J, Nikolaev AR, Van Leeuwen C. Spatial and temporal structure of phase synchronization of spontaneous alpha EEG activity. Biol Cybern. 2005;92(1):54-60. doi:10.1007/S00422-004-0533-Z

78. Wascher E, Rasch B, Sänger J, et al. Frontal theta activity reflects distinct aspects of mental fatigue. Biol Psychol. 2014;96(1):57-65. doi:10.1016/J.BIOPSYCHO.2013.11.010

79. Cheng S-Y, Hsu H-T. Mental Fatigue Measurement Using EEG. undefined. Published online July 28, 2011. doi:10.5772/16376

80. Benedek M, Schickel RJ, Jauk E, Fink A, Neubauer AC. Alpha power increases in right parietal cortex reflects focused internal attention. Neuropsychologia. 2014;56(1):393-400. doi:10.1016/j.neuropsychologia.2014.02.010

81. Cavanagh JF, Frank MJ. Frontal theta as a mechanism for cognitive control. Trends Cogn Sci. 2014;18(8):414. doi:10.1016/J.TICS.2014.04.012

82. Zavala B, Jang A, Trotta M, Lungu CI, Brown P, Zaghloul KA. Cognitive control involves theta power within trials and beta power across trials in the prefrontal-subthalamic network. Brain. 2018;141(12):3361-3376. doi:10.1093/BRAIN/AWY266

83. Coan JA, Allen JJB. Frontal EEG asymmetry as a moderator and mediator of emotion. Biol Psychol. 2004;67(1-2):7-50. doi:10.1016/J.BIOPSYCHO.2004.03.002

84. Harmon-Jones E, Gable PA, Peterson CK. The role of asymmetric frontal cortical activity in emotion-related phenomena: A review and update. Biol Psychol. 2010;84(3):451-462. doi:10.1016/J.BIOPSYCHO.2009.08.010

85. Davidson RJ, Chapman JP, Chapman LJ, Henriques JB. Asymmetrical Brain Electrical Activity Discriminates Between Psychometrically-Matched Verbal and Spatial Cognitive Tasks. Psychophysiology. 1990;27(5):528-543. doi:10.1111/J.1469-8986.1990.TB01970.X

86. Cook IA, O'Hara R, Uijtdehaage SHJ, Mandelkern M, Leuchter AF. Assessing the accuracy of topographic EEG mapping for determining local brain function. Electroencephalogr Clin Neurophysiol. 1998;107(6):408-414. doi:10.1016/S0013-4694(98)00092-3

87. Dunkley BT, Da Costa L, Bethune A, et al. Low-frequency connectivity is associated with mild traumatic brain injury. NeuroImage Clin. 2015;7:611-621. doi:10.1016/J.NICL.2015.02.020

88. Moore RD, Sauve W, Ellemberg D. Neurophysiological correlates of persistent psycho-affective alterations in athletes with a history of concussion. Brain Imaging Behav. 2016;10(4):1108-1116. doi:10.1007/s11682-015-9473-6

89. Schmidt MT, Kanda PAM, Basile LFH, et al. Index of Alpha/Theta Ratio of the Electroencephalogram: A New Marker for Alzheimer's Disease. Front Aging Neurosci. 2013;5(OCT). doi:10.3389/FNAGI.2013.00060

90. Gorman LK, Fu K, Hovda DA, Murray M, Traystman RJ. Effects of traumatic brain injury on the cholinergic system in the rat. J Neurotrauma. 1996;13(8):457-463. doi:10.1089/NEU.1996.13.457

91. Davies P, Maloney AJF. SELECTIVE LOSS OF CENTRAL CHOLINERGIC NEURONS IN ALZHEIMER'S DISEASE. Lancet. 1976;308(8000):1403. doi:10.1016/S0140-6736(76)91936-X

92. Pratap-Chand R, Sinniah M, Salem FA. Cognitive evoked potential (P300): a metric for cerebral concussion. Acta Neurol Scand. 1988;78(3):185-189. doi:10.1111/J.1600-0404.1988.TB03643.X

93. Watson MR, Fenton GW, McClelland RJ, Lumsden J, Headley M, Rutherford WH. The post-concussional state: neurophysiological aspects. Br J Psychiatry. 1995;167(4):514-521. doi:10.1192/BJP.167.4.514

94. D. Gordon E. Robertson, Graham E. Caldwell, Joseph Hamill, Gary Kamen SNW. Reasearch Methods in Biomechanics.; 2014.

95. Jurkat-Rott K, Lerche H, Weber Y, Lehmann-Horn F. Hereditary Channelopathies in Neurology. In: Advances in Experimental Medicine and Biology. Vol 686. ; 2010:305-334. doi:10.1007/978-90-481-9485-8_18

96. Harrison PJ. The relationship between the distribution of motor unit mechanical properties and the forces due to recruitment and to rate coding for the generation of muscle force. Brain Res. 1983;264(2):311-315. doi:10.1016/0006-8993(83)90831-4

97. Moritani T, Muro M, Nagata A. Intramuscular and surface electromyogram changes during muscle fatigue. J Appl Physiol. 1986;60(4):1179-1185. doi:10.1152/jappl.1986.60.4.1179

98. Scholz E, Diener HC, Noth J, Friedemann H, Dichgans J, Bacher M. Medium and long latency EMG responses in leg muscles: Parkinson's disease. J Neurol Neurosurg Psychiatry. 1987;50(1):66-70. doi:10.1136/jnnp.50.1.66

99. Mima T, Hallett M. Corticomuscular coherence: a review. J Clin Neurophysiol. 1999;16(6):501-511. Accessed March 22, 2019. http://www.ncbi.nlm.nih.gov/pubmed/10600018

100. Mima T, Steger J, Schulman AE, Gerloff C, Hallett M. Electroencephalographic measurement of motor cortex control of muscle activity in humans. Clin Neurophysiol. 2000;111(2):326-337. doi:10.1016/S1388-2457(99)00229-1

101. Vecchio F, Del Percio C, Marzano N, et al. Functional cortico-muscular coupling during upright standing in athletes and nonathletes: A coherence electroencephalographic-electromyographic study. Behav Neurosci. 2008;122(4):917-927. doi:10.1037/0735-7044.122.4.917

102. Hansen S, Hansen NL, Christensen LOD, Petersen NT, Nielsen JB. Coupling of antagonistic ankle muscles during co-contraction in humans. Exp Brain Res. 2002;146(3):282-292. doi:10.1007/s00221-002-1152-3

103. Gwin JT, Ferris DP. Beta- and gamma-range human lower limb corticomuscular coherence. Front Hum Neurosci. 2012;6:258. doi:10.3389/fnhum.2012.00258

104. Schoffelen J-M, Poort J, Oostenveld R, Fries P. Selective Movement Preparation Is Subserved by Selective Increases in Corticomuscular Gamma-Band Coherence. J Neurosci. 2011;31(18):6750-6758. doi:10.1523/JNEUROSCI.4882-10.2011

105. Omlor W, Patino L, Hepp-Reymond M-C, Kristeva R. Gamma-range corticomuscular coherence during dynamic force output. Neuroimage. 2007;34(3):1191-1198. doi:10.1016/j.neuroimage.2006.10.018

106. Halliday DM, Farmer SF. On the Need for Rectification of Surface EMG. J Neurophysiol. 2010;103(6):3547-3547. doi:10.1152/jn.00222.2010

107. McClelland VM, Cvetkovic Z, Mills KR. Inconsistent effects of EMG rectification on coherence analysis. J Physiol. 2014;592(1):249-250. doi:10.1113/jphysiol.2013.265181

108. Myers L., Lowery M, O'Malley M, et al. Rectification and non-linear pre-processing of EMG signals for cortico-muscular analysis. J Neurosci Methods. 2003;124(2):157-165. doi:10.1016/S0165-0270(03)00004-9

109. Levy DL, Mendell NR, Holzman PS. The antisaccade task and neuropsychological tests of prefrontal cortical integrity in schizophrenia: empirical findings and interpretative considerations. World Psychiatry. 2004;3(1):32-40. Accessed March 23, 2019. http://www.ncbi.nlm.nih.gov/pubmed/16633452

110. Maruta J, Heaton KJ, Maule AL, Ghajar J. Predictive Visual Tracking: Specificity in Mild Traumatic Brain Injury and Sleep Deprivation. Mil Med. 2014;179(6):619-625. doi:10.7205/MILMED-D-13-00420

111. Bellman RE, Zadeh LA. Decision-Making in a Fuzzy Environment. Manage Sci. 1970;17(4):B-141-B-164. doi:10.1287/mnsc.17.4.b141

112. Greeno JG. Gibson's Affordances. Psychol Rev. 1994;101(2):336-342. Accessed March 26, 2019. http://ftp.idiap.ch/pub/courses/EE-700/material/31-10-2012/gibsonAffordances.pdf

113. Hick WE. On the Rate of Gain of Information. Q J Exp Psychol. 2008;4(1):11-26. doi:10.1080/17470215208416600

114. Fitts PM. The information capacity of the human motor system in controlling the amplitude of movement. J Exp Psychol. 1954;47(6):381-391. doi:10.1037/h0055392

115. Fitts P, Posner M. Human Performance: Basic Concepts in Psychology. 1st ed. Praeger; 1967.

116. Shaver TK, Ozga JE, Zhu B, Anderson KG, Martens KM, Vonder Haar C. Long-term deficits in risky decision-making after traumatic brain injury on a rat analog of the Iowa gambling task. Brain Res. 2019;1704:103-113. doi:10.1016/j.brainres.2018.10.004

117. Levine B, Black SE, Cheung G, Campbell A, O'Toole C, Schwartz ML. Gambling task performance in traumatic brain injury: relationships to injury severity, atrophy, lesion location, and cognitive and psychosocial outcome. Cogn Behav Neurol. 2005;18(1):45-54. Accessed March 26, 2019. http://www.ncbi.nlm.nih.gov/pubmed/15761276

118. Cardoso CO, Cotrena C, Grassi-Oliveira R, Zimmermann N, Fonseca RP, Branco LD. Impaired decision-making after traumatic brain injury: The Iowa Gambling Task. Brain Inj. 2014;28(8):1070-1075. doi:10.3109/02699052.2014.896943

119. Ho RA, Hall GB, Noseworthy MD, DeMatteo C. An Emotional Go/No-Go fMRI study in adolescents with depressive symptoms following concussion. Int J Psychophysiol. 2018;132:62-73. doi:10.1016/j.ijpsycho.2017.09.021

120. Howell DR, Meehan WP, Barber Foss KD, Reches A, Weiss M, Myer GD. Reduced dual-task gait speed is associated with visual Go/No-Go brain network activation in children and adolescents with concussion. Brain Inj. 2018;32(9):1129-1134. doi:10.1080/02699052.2018.1482424

121. Dichter GS, Felder JN, Smoski MJ. Affective context interferes with cognitive control in unipolar depression: An fMRI investigation. J Affect Disord. 2009;114(1-3):131-142. doi:10.1016/j.jad.2008.06.027

122. Gordon KE, Dooley JM, Wood EP. Descriptive Epidemiology of Concussion. Pediatr Neurol. 2006;34(5):376-378. doi:10.1016/J.PEDIATRNEUROL.2005.09.007

123. Bahill AT, Clark MR, Stark L. The main sequence, a tool for studying human eye movements. Math Biosci. 1975;24(3-4):191-204. doi:10.1016/0025-5564(75)90075-9

124. Cochrane GD, Christy JB, Almutairi A, Busettini C, Swanson MW, Weise KK. Visuo-oculomotor Function and Reaction Times in Athletes with and without Concussion. Optom Vis Sci. 2019;96(4):256. doi:10.1097/OPX.0000000000001364

125. Tommerdahl M, Francisco E, Holden J, et al. An Accurate Measure of Reaction Time can Provide Objective Metrics of Concussion. J Sci Med. 2020;2(2). doi:10.37714/JOSAM.V2I2.31

126. Cavanaugh JT, Mercer VS, Stergiou N. Approximate entropy detects the effect of a secondary cognitive task on postural control in healthy young adults: A methodological report. J Neuroeng Rehabil. 2007;4(1):1-7. doi:10.1186/1743-0003-4-42

127. Roerdink M, De Haart M, Daffertshofer A, Donker SF, Geurts ACH, Beek PJ. Dynamical structure of center-of-pressure trajectories in patients recovering from stroke. Exp Brain Res. 2006;174(2):256-269. doi:10.1007/s00221-006-0441-7

128. Dunkley BT, Urban K, Da Costa L, Wong SM, Pang EW, Taylor MJ. Default mode network oscillatory coupling is increased following concussion. Front Neurol. 2018;9(APR):280. doi:10.3389/FNEUR.2018.00280/BIBTEX

129. Sakamoto A, Sinclair PJ, Moritani T. Muscle activations under varying lifting speeds and intensities during bench press. Eur J Appl Physiol. 2012;112(3):1015-1025. doi:10.1007/s00421-011-2059-0

130. Evetovich TK, Housh TJ, Johnson GO, Smith DB, Ebersole KT, Perry SR. Gender comparisons of the mechanomyographic responses to maximal concentric and eccentric isokinetic muscle actions. Med Sci Sports Exerc. 1998;30(12):1697-1702. doi:10.1097/00005768-199812000-00007

131. Witham CL, Riddle CN, Baker MR, Baker SN. Contributions of descending and ascending pathways to corticomuscular coherence in humans. J Physiol. 2011;589(15):3789-3800. doi:10.1113/jphysiol.2011.211045

132. Ebersole KT, Housh TJ, Weir JP, Johnson GO, Evetovich TK, Smith DB. The effects of leg angular velocity on mean power frequency and amplitude of the mechanomyographic signal. Electromyogr Clin Neurophysiol. 2000;40(1):49-55. Accessed July 13, 2022. https://europepmc.org/article/med/10782358

133. Beck TW, Housh TJ, Cramer JT, et al. Mechnomyographic amplitude and frequency responses during dynamic muscle actions: A comprehensive review. Biomed Eng Online. 2005;4(1):1-27. doi:10.1186/1475-925X-4-67

134. Buckley TA, Vallabhajosula S, Oldham JR, et al. Evidence of a conservative gait strategy in athletes with a history of concussions. J Sport Heal Sci. 2016;5(4):417-423. doi:10.1016/j.jshs.2015.03.010

135. Clay V, König P, König S. Eye Tracking in Virtual Reality. J Eye Mov Res. 2019;12(1). doi:10.16910/JEMR.12.1.3

136. Benedek M, Schickel RJ, Jauk E, Fink A, Neubauer AC. Alpha power increases in right parietal cortex reflects focused internal attention. Neuropsychologia. 2014;56(100):393-400. doi:10.1016/J.NEUROPSYCHOLOGIA.2014.02.010

137. Butz M, Wörgötter F, van Ooyen A. Activity-dependent structural plasticity. Brain Res Rev. 2009;60(2):287-305. doi:10.1016/J.BRAINRESREV.2008.12.023

138. Maki BE, Holliday PJ, Topper AK. A prospective study of postural balance and risk of falling in an ambulatory and independent elderly population. Journals Gerontol. 1994;49(2):M72-M84. doi:10.1093/geronj/49.2.M72

139. Carpenter MG, Frank JS, Silcher CP, Peysar GW. The influence of postural threat on the control of upright stance. Exp Brain Res. 2001;138(2):210-218. doi:10.1007/s002210100681

140. Kouzaki M, Shinohara M. Steadiness in plantar flexor muscles and its relation to postural sway in young and elderly adults. Muscle and Nerve. 2010;42(1):78-87. doi:10.1002/mus.21599

APPENDIX: SUPPORTING DOCUMENTS

1. Concussion Screening Questionnaire

Age ________________________________

Race: ☐ Caucasian ☐ Afro-American ☐ Hispanic ☐ Asian/Pacific ☐ Alaskan/Indian ☐ Other __________

Sport(s) ________________________________ Position(s) ________________________________

Height ____________ Weight ______________ ☐ Right Handed ☐ Left Handed

Head Injuries / Concussion:

History of Head Injury / Concussion Injury? ☐ YES ☐ NO

- List Dates (month and year, if know)________________________________

- Please Describe ________________________________

Were Any Diagnostic Tests Performed? ☐ YES ☐ NO (check all that apply)

☐ MRI ☐ CT-Scan ☐ Neuropsychological Testing ☐ Other ________________

Have You Ever Been Hospitalized, Knocked Out, Become Unconscious, and/or Lost Your Memory Due To A Head Injury / Concussion? ☐ YES ☐ NO

Do You Suffer From Headaches? ☐ YES ☐ NO

- When? ☐ Every Day ☐ 1-2 Times/Week ☐ 1-2 Times/Month
- Where Are Your Headaches Located? ☐ Left Side of Head ☐ Right Side of Head ☐ Front of Head ☐ Back of Head ☐ All Over Your Head

Do You Have A History of Migraine Headaches? ☐ YES ☐ NO

- How Often ____________________ Please Describe ________________

- Medications Taken for Migraines? ________________________________

Have You Had Headaches For More Than Three (3) Months? ☐ YES ☐ NO

- If yes, please explain ________________________________

Eyes:

Do you routinely wear glasses? ☐ YES ☐ NO

Do you routinely wear contact lenses? ☐ YES ☐ NO

- Prescription?________________________________

2. International Physical Activity Questionnaire – Short Version 7 Days Self-Administered

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

3. IRB Approval Memoranda

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** · **rede.ecu.edu/umcirb/**

Notification of Initial Approval: Expedited

From: Biomedical IRB
To: Nicholas Murray
CC:

Date: 8/28/2019
Re: UMCIRB 19-001532
Virtual Reality as a Means for Concussion Testing

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) occurred on 8/27/2019. 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.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a Final Report application to the UMCIRB prior to the Expected End Date provided in the IRB application. If the study is not completed by this date, an Amendment will need to be submitted to extend the Expected End Date. The Investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Name	Description
Concussion history screen.docx	Surveys and Questionnaires
Informed Consent Form.doc	Consent Forms

Recruitment scripts.docx	Recruitment Documents/Scripts
Research protocol.docx	Study Protocol or Grant Application
study flyer.docx	Recruitment Documents/Scripts

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** · **rede.ecu.edu/umcirb/**

Notification of Initial Approval: Expedited

From: Biomedical IRB
To: Gustavo Sandri Heidner
CC: Nicholas Murray
Nicholas Murray
Date: 3/4/2020
Re: UMCIRB 20-000312
Investigation of long-lasting oculomotor impairment and injury prevalence in mTBI subjects

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) occurred on 3/3/2020. 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.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a Final Report application to the UMCIRB prior to the Expected End Date provided in the IRB application. If the study is not completed by this date, an Amendment will need to be submitted to extend the Expected End Date. The Investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Name	Description
Background and Protocol	Study Protocol or Grant Application
concussion history survey.docx	Surveys and Questionnaires
Informed Consent Form AIM 3.doc	Consent Forms
IPAQ_English_self-admin_short.pdf	Surveys and Questionnaires
Lower Extremity Injury Questionnarie.doc	Surveys and Questionnaires
Recruitment scripts (1).docx	Recruitment Documents/Scripts
SCAT3.pdf	Surveys and Questionnaires
study flyer (1).docx	Recruitment Documents/Scripts

For research studies where a waiver of HIPAA Authorization has been approved, each of the waiver criteria in 45 CFR 164.512(i)(2)(ii) has been met. Additionally, the elements of PHI to be collected as described in items 1 and 2 of the Application for Waiver of Authorization have been determined to be the minimal necessary for the specified research.

The Chairperson (or designee) does not have a potential for conflict of interest on this study.