THE EFFECT OF ACTIVE TRAINING ON CLINICAL AND PHYSIOLOGICAL OUTCOMES IN HEALTHY AND CONCUSSED COLLEGE-AGED PARTICIPANTS

Elizabeth Fay Teel

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Human Movement Science Curriculum in the School of Medicine.

Chapel Hill
2017

Approved by:

Jason P. Mihalik

L. Gregory Appelbaum

Claudio L. Battaglini

Kevin M. Guskiewicz

Stephen W. Marshall

Johna K. Register-Mihalik

ABSTRACT

Elizabeth Fay Teel: The Effect of ACTIVE Training on Clinical and Physiological Outcomes in Healthy and Concussed College-Aged Participants
(Under the direction of Jason P. Mihalik)

Concussions are a pathophysiological injury resulting in symptom, clinical, and physiological deficits. Current guidelines dictate complete physical rest until asymptomatic but a shift towards more active recovery is being advised. Exercise as rehabilitation has been successful in patients with chronic concussion dysfunction, but has not been thoroughly studied acutely following injury. The expected changes of brief aerobic training on clinical and physiological outcomes remain unknown. The ***a***cute ***c***oncussion ***t***herapy ***i***nter***ve***ntion (ACTIVE) training is an aerobic exercise program designed to expedite clinical and physiological healing following concussion, but first must be vetted in healthy populations. The primary purpose of this study was to evaluate the feasibility and effectiveness of ACTIVE training in healthy college-aged participants. Participants were randomly assigned to ACTIVE training or control groups. All participants received clinical and physiological assessments at two test sessions approximately 14 days apart. ACTIVE training participants completed six training bouts between test sessions. ACTIVE training was feasible, with no adverse events reported and high adherence to the progressively increasing training protocol. Heart rate (P=0.01), percentage of predicted maximal heart rate (P=0.01), and test duration (P=0.03) significantly increased in the intervention group between test sessions. The intervention group had significantly increased central alpha power between sessions and higher central theta compared to the control group (p=0.02) during eyes closed (p=0.006) conditions. Clinical outcomes were stable in response to ACTIVE training, with no mean differences exceeding reliable change scores. These

cardiopulmonary improvements provide an important proof of concept in translating ACTIVE training to concussed patients, suggesting that aerobic training may target the physiological domains affected following concussion and help athletes maintain fitness during recovery. EEG outcomes may represent the neural underpinning of psychological and cognitive domains, which may have additional relevance to concussed populations and should be studied further in the future. The stability of clinical variables following ACTIVE training highlights their utility as diagnostic and management tools, as any changes seen in these assessments following injury represents subsequent healing and are not a byproduct of exercise alone.

Mom: Thank you for always being my biggest cheerleader, for your unwavering support, and for giving me the space to grow into my own person. I hope you know that I do, and always have, appreciated all the sacrifices you made for me.

Dad: Thank you for being my guardian angel, for teaching me to be independent, and setting a pristine example of hard work. I will continue to miss you everyday, but take comfort in that fact that you'll be watching over me until I see you again.

I am a firm believer that family are not the people who share your DNA, but the people who love you at your worst and support you at your weakest. To all the people I consider family: I could have never made it here without you. I can never express my joy and gratitude for having you in my life, so I will just say thank you for everything. This dissertation is dedicated to all of you.

ACKNOWLEDGEMENTS

Many people contributed their support, guidance, and expertise, making this project possible. Dr. Jason Mihalik, thank you for being a great mentor, colleague, and friend throughout this process. Your ability to push me while reining my big ideas into a feasible project was second to none. I am sure there were many a time when you wished you had not moved offices just so I would stop popping my head in, but I appreciate your patience and guidance throughout this process.

This dissertation is the result of a true team effort. To Drs. Greg Appelbaum, Claudio Battaglini, Kevin Guskiewicz, Steve Marshall, and Johna Register-Mihalik: thank you for all the time and knowledge you contributed to make this project a success. Each of you played a unique and vital role in this project and I am eternally grateful for your guidance. I would also like to acknowledge Drs. Kevin Carneiro, Erik Hanson, and Shabbar Ranapurwala, who graciously offered their time to assist with various aspects of this study.

This project was not without its share of ups and downs. A huge thank you to #TeamGfeller for keeping my spirits up and sanity intact throughout this project. I appreciate all of your help throughout this process, whether it was jumping in to assist with data collection or making me laugh.

This study required exponentially more manpower than I could contribute alone. A huge thank you to Grant Cabell, Madison Harper, Erin Leasure, and Austin White for being the best research assistants a girl could ask for.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BESS	Balance Error Scoring System
CNS	CNS Vital Signs
EEG	Electroencephalography
GSC	Graded Symptom Checklist
ICC	Intraclass Correlation Coefficient
PCS	Post-Concussion Syndrome
qEEG	Quantitative Electroencephalography
RER	Respiratory Exchange Rate
S100B	S100 Calcium-Binding Protein B
SAC	Standardized Assessment of Concussion
VOMS	Vestibular/Ocular Motor Screening
VOR	Vestibulo-Ocular Reflex
VO_{2max}	Maximal Oxygen Consumption

CHAPTER 1

SPECIFIC AIMS

Rehabilitating the nearly 4 million athletes concussed every year[1] remains challenging as current consensus guidelines advocate only for complete cognitive and physical rest. For 500,000 individuals each year, rest alone is insufficient to promote full concussion recovery, resulting in prolonged symptoms and physical,[2] academic,[3,4] and psychosocial consequences.[3] *Active rehabilitation applied earlier in the recovery process may expedite recovery and mitigate negative sequelae associated with concussion*. Exercise as rehabilitation is successful in reducing chronic concussive symptoms and deficits,[5-8] but the effectiveness of these interventions is based solely on clinical outcomes. Concussions are increasing defined as a pathophysiologic injury[9] and physiological assessments, such as electroencephalographs (EEG) and maximal exercise testing, may provide clinicians with information about the neural and metabolic underpinnings driving clinical deficits. However, the recommendations for complete physical rest until asymptomatic have prevented researchers from investigating the mechanisms through which exercise training influences physiological assessments and how this may relate to functional recovery acutely after injury. Understanding how rehabilitation interventions may differentially affect healthy and concussed individuals is critical to understanding recovery factors that can be utilized to actively promote functional and physiological healing following concussion, providing clinicians with feasible tools to expedite the recovery process and minimize the deleterious consequences of prolonged concussion recovery.

Our *long-term goal* is to promote full concussion recovery, by eliminating immediate

deficits, lessening future injury risk, and reducing associated co-morbidities. The *overall objective* of this R01 proposal is to evaluate the effect of ***a****cute* ***c****oncussion* ***t****herapy* ***i****nter****ve****ntion* (ACTIVE) training on clinical and physiological outcomes in healthy and concussed individuals and to determine the safety and feasibility of ACTIVE training. Our *central hypothesis* is that ACTIVE training is a safe and feasible intervention that will significantly improve clinical and physiological measures in healthy and concussed subjects. Our *approach* will be to randomly assign healthy and concussed participants to ACTIVE training (intervention) or control (no intervention) groups. Participants, regardless of group assignment, will receive clinical concussion and physiological assessments at study outset. Concussed participants in the intervention group will begin stationary cycle ergometer workouts starting three days post-injury, while the control group will follow physician guidelines for rest and activity. Healthy participants will complete six ACTIVE training sessions, while concussed participants will complete ACTIVE training at least three days per week until asymptomatic. Participants will repeat the clinical concussion and physiological assessment battery prior to study termination. Our *rationale* for assessing the effectiveness of ACTIVE training is that successful completion of this work will describe normal changes in clinical and physiological measures following a brief aerobic training intervention in healthy individuals and will elucidate rehabilitation paradigms designed to improve clinical and physiological outcomes in concussed participants, allowing them to return to the academic and athletic endeavors sooner while enhancing athlete safety.

Aim 1. To test the hypothesis that healthy college-aged participants randomized to ACTIVE training will have significantly improved symptom, balance, and cognition, but not vision, outcomes compared to healthy college-aged participants randomized to the control group.

Aim 2. To test the hypothesis that healthy college-aged participants randomized to ACTIVE training will have significantly improved resting-state EEG and cardiopulmonary

outcomes compared to healthy college-aged participants in the control group.

Aim 3. To test the hypothesis that ACTIVE training is safe and feasible in college-aged participants.

Exploratory Aims. To explore the hypothesis that ACTIVE training is a safe and feasible intervention for acutely concussed individuals and that concussed individuals randomized to ACTIVE training will demonstrate significant improvements on all clinical and physiological outcomes compared to concussed individuals randomized to the control group.

As researchers begin to evaluate concussion rehabilitation interventions applied in the acute recovery period to enhance healing, how these interventions may influence both clinical and physiological outcomes in healthy and injured populations remains unknown. We expect our work to: 1) determine how ACTIVE training influences clinical and physiological measures in healthy subjects, 2) determine the safety and feasibility of ACTIVE training in healthy populations, and 3) explore the safety, feasibility, and effectiveness of ACTIVE training in improving clinical and physiological outcomes among acutely concussed individuals. The positive impact of this work is to identify feasible concussion rehabilitation strategies that can be implemented acutely after injury to enhance athlete safety, eliminate immediate concussive deficits, and reduce the risk of recurrent injury and co-morbidities associated with prolonged concussion recovery.

——————————PRIMARY STUDY: HEALTHY PARTICIPANTS——————————

A) SIGNIFICANCE

Up to 500,000 individuals[10] every year fail to fully recover from concussion with rest alone and show persistent symptomatic, cognitive, balance, and physiological deficits for months following injury.[11] Experts are beginning to shift from more traditional rest recommendations following injury[12] towards more active recovery strategies.[13] Exercise as concussion rehabilitation is effective in improving symptomatic and clinical deficits in the chronic

phases of recovery,[6,14] but the effectiveness of these programs has not been thoroughly studied in acute recovery stages or in relation to physiological outcomes. Exercise paradigms must be vetted in a healthy population in order to ensure the intervention is safe, feasible, and targets intended outcomes before being implemented in concussed populations. *This research contributes knowledge related to the safety, feasibility, and effectiveness of a two-week exercise intervention program (**a**cute **c**oncussion **t**herapy **i**nter**ve**ntion (ACTIVE) training) in a healthy, college-aged population.* We believe that ACTIVE training will be a safe and feasible intervention and will improve symptom, cognitive, balance, and physiological markers in healthy participants. Initially, this would allow researchers to implement the protocol with acutely concussed participants and determine the effect of ACTIVE training on concussion recovery. Feasible rehabilitation programs implemented acutely following injury targeting multiple deficits/domains may greatly improve patient quality of life by reducing the human and financial burdens associated with a compartmentalized multi-provider continuum of care employed to individually rehabilitate each deficit type. *Future R series studies (e.g. R01, R03, R21) can investigate the optimal frequency, duration, and intensity of exercise to create the most effective intervention and longitudinal studies can evaluate if ACTIVE training reduces the risk for negative academic, social, and physiological consequences of concussion, recurrent injury, and late-life consequences associated with repetitive head trauma*.

B) INNOVATION

Athletes who return too quickly are at risk for recurrent concussion, the majority occurring within 10 days of initial injury.[15] A history of multiple concussions is increasingly linked to late-life consequences and, although exceedingly rare, multiple head injuries in a short timespan can lead to catastrophic injury or death.[16] Researchers have developed objective clinical tests to increase the sensitivity of concussion diagnosis to circumvent the 80% of collegiate athletes who attempt to mask concussions.[17] Current best practice recommends a

combination of symptom, cognitive, and balance assessments prior to the start of an athletic season (pre-season) to ascertain baseline levels of functioning for each athlete. These evaluations are then repeated after a potential injury in order to assist with diagnosis. Several weeks to months may pass between a pre-season baseline and potential concussion, during which athletes often complete aerobic exercise training as part of athletic practices and competition. Persistent aerobic activity improves cognitive[18] and physiological[19] domains, but it remains unknown if these changes are detectable on clinical concussion assessments (**Figure 1.1**). Clinical concussion assessments are also concerning because of their limitations including learning effects and sandbagging. Stable physiological measures unaffected by motivation complement clinical assessments by evading these shortcomings;[20] however they have rarely been utilized.

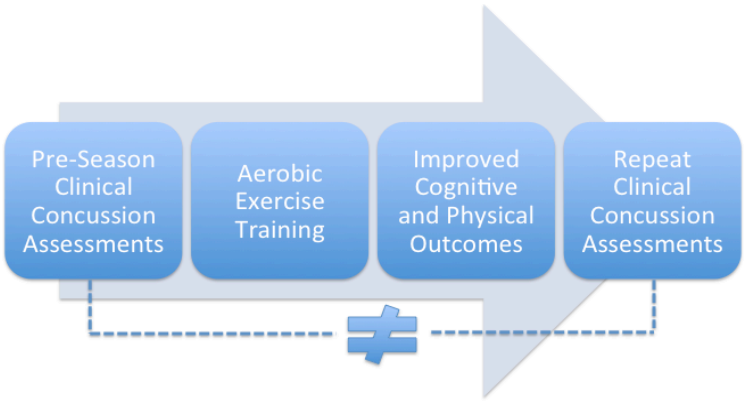


Figure 1.1. Current best practice recommends an athlete undergo a pre-season concussion baseline prior to athletic participation. As participants begin practices and competition for their respective sport, levels of physical activity increase. Increased aerobic training is known to decrease emotional symptoms and improve cognition and postural control. What remains unknown is these improvements are detectable using clinical concussion assessments, which can have critical implications for concussion diagnosis and management.

The proposed study is novel because it will evaluate the stability of clinical concussion assessment tools in response to an exercise-training program. Concussed individuals often display cognitive and balance deficits following injuries,[21] leading researchers to develop objective clinical tools to assess these domains. In healthy populations, an acute exercise session is known to negatively effect outcomes on concussion assessment tools.[22,23] Conversely, aerobic training programs globally improve many aspects of cognition[18] and postural control,[24] but *what remains unknown is whether clinical concussion assessment tools are sensitive to changes in response to aerobic exercise training in healthy individuals*. Athletes

commonly participate in long-term aerobic exercise as part of their sport training. If clinical concussion assessment tools change in response to aerobic training, current clinical recommendations for directly comparing pre-season baseline scores to outcomes after potential injury may not be the most appropriate method for diagnostic decisions and may unintentionally jeopardize athlete safety.

The effectiveness of ACTIVE training in improving physiological measures will be investigated in this study. Many consensus groups define concussion as a pathophysiological injury,[9] yet *no physiological measures are recommended as part of the clinical concussion assessment battery*. Physiological markers, such as resting-state electroencephalography (rs-EEG) outcomes and cardiopulmonary variables, may provide valuable insight into the neural and metabolic underpinnings of concussion and be useful in clinical diagnosis and management. *Normative data for rs-EEG and physiological outcomes and how they are influenced by exercise are necessary to understand before these measures can be used to manage concussed patients.* These data may also serve as the basis for future exercise prescription guidelines to maximize concussion recovery while prioritizing safety.

C) APPROACH FOR AIMS 1-3

Healthy participants will be recruited from sport clubs, intramural sports, and the general student population at the University of North Carolina at Chapel Hill (UNC) and will be randomized into ACTIVE training (intervention) or control (no intervention) groups in a blocked procedure with block sizes of four. All participants will undergo clinical (symptom reporting, neurocognitive testing, balance assessment, and vision evaluation) and physiological (rs-EEG and cardiopulmonary) assessment batteries at two times during the study. Healthy participants randomized into the intervention group will complete the second assessment battery following 6 aerobic exercise-training sessions over 10-14 days. Control participants will complete identical clinical/physiological assessments over the same temporal window, but will receive no

intervention between assessments (**Figure 1.2**). Outcome measures related to study procedures and the intervention itself will be collected during study participation to determine protocol feasibility. Study participation will end after the second assessment. Our *central hypothesis* is that healthy ACTIVE training participants will significantly improve on clinical and physiological outcomes compared to individuals randomized to the control group (Aims 1 & 2) and that this intervention will be safe and feasible (Aim 3).

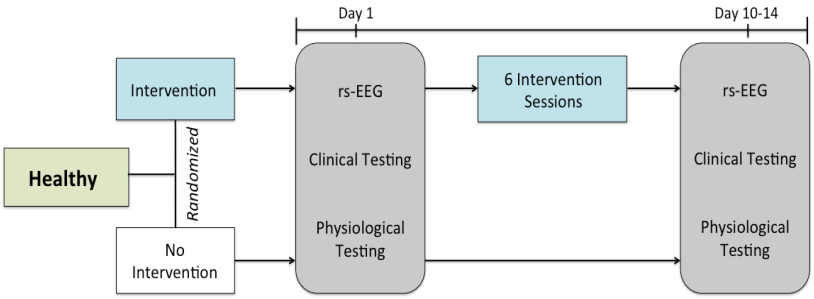


Figure 1.2. Healthy participants will be randomized to exercise training (intervention) or control (no intervention) groups. Each group will complete identical clinical and physiological assessments batteries 10-14 days apart. The intervention group will complete 6 intervention sessions between

Recruitment and consent. Healthy participants will be contacted through recruitment flyers and emails approved by UNC's IRB board. A research team member will then approach interested individuals to explain the goals of this study and screen for eligibility. Eligible individuals interested in participating will sign appropriate consent forms during this initial meeting. Participants will be randomized immediately after providing informed consent. Each research team member has at least seven years of experience completing clinical research with this population and at least one member of the research team has considerable expertise in each of the outcome measures used in this study.

C1) Aim 1. To test the hypothesis that healthy college-aged participants randomized to ACTIVE training will have significantly improved symptoms, balance, and cognition, but not vision, outcomes compared to healthy college-aged participants randomized to the control group. *Participants will complete two identical clinical assessment batteries: neurocognition (CNS Vital Signs, Standard Assessment of Concussion), balance (Balance Error Scoring System), vision (Vestibular/Ocular Motor Screening), and symptoms*

(Graded Symptom Checklist). Healthy participants randomized into the intervention group will perform 6 training sessions over a 10-14 day period between clinical assessments, while the control group will complete the second assessment in the same time window as the training group without any intervention between sessions. Most collegiate students recover from concussion within two weeks and ACTIVE training is to be completed 3 days per week in concussed populations; therefore, 6 training sessions over 10-14 days were selected for the healthy intervention group to approximate training session frequency and time between assessments concussed participants will likely experience. We hypothesize that healthy participants randomized to ACTIVE training will show significantly improved clinical outcomes, with the exception of near-point convergence, compared to the no intervention group.

C1a) Clinical concussion assessments and exercise. Clinical assessments traditionally used in concussion care have been evaluated in non-concussed samples following a single-bout of exercise. In uninjured populations, concussion-like symptoms increase immediately following exercise and remain elevated up to 15 minutes,[25,26] but emotional symptoms improve (decrease) following aerobic training.[27] Verbal memory deficits exist following a maximal exercise test, but no differences in visual memory, motor processing, and reaction time domains were found.[23] Balance deficits, measured by the Balance Error Scoring System, are present following exercise and persist up to 20 minutes post-activity.[22,28] In healthy populations, persistent aerobic exercise, as opposed to acute sessions of activity, improves depression scores[29] and cognition.[18] However, these improvements are seen using general emotional and neuropsychological scales and have not been evaluated on assessments traditionally used in concussion care. Athletes complete aerobic exercise for sport training between pre-season baseline and potential injury evaluations. Understanding the effects aerobic training has on clinical concussion measures can have high clinical relevance to ensure proper diagnoses are made and athlete safety is prioritized.

C1b) The equipment, assessments, and outcomes associated with *Aim 1* are listed below.

Figure 1.3. Lode Corival Cycle Ergometer (750-watt) that will be used during incremental cycle ergometer and intervention sessions.

Cycle ergometer. A Lode Corival Cycle Ergometer (Lode, Gronigen, The Netherlands) will be used for the maximal exercise test and all intervention sessions (**Figure 1.3**). The Corival is controlled by an eddy current electro-magnetic braking mechanism that ensures that the participant exercises at a consistent workload regardless of the revolutions per minute he/she cycles at. Cardiopulmonary outcomes during maximal exercise are reproducible and reliable when using this cycle ergometer.[30]

Maximal exercise test protocol. All participants will complete two maximal exercise tests. The participant's workload (in Watts) at termination during the first session will be used to create individualized exercise intensities for the ACTIVE training sessions. ACTIVE training is implemented in the acute recovery stage and utilizes stationary cycle ergometers, as opposed to treadmill protocols used in other studies,[5,6] to enhance participant safety and maximize accuracy of the exercise prescription. All concussed and healthy participants will complete exertion testing and intervention sessions on the cycle ergometer in order to maintain consistency between groups. **Table 1.1** depicts the protocol for the maximal exercise test. Participant's heart rate and rate of perceived exertion will be monitored prior to exercise, every minute during the protocol, and at

Table 1.1. Maximal exercise test protocol for healthy participants. Workload (watts) at protocol termination will determine individualized exercise intensity for ACTIVE training sessions.

Maximal Exercise Test
0:00- Begin pedaling at 50W workload
2:00- Workload increased to 100W
4:00- Workload increased to 150W
6:00- Workload increased to 180W
8:00- Workload increased to 210W
10:00- Workload increased to 240W
Every minute following, workload increased by 30W
Termination- Volitional fatigue

protocol termination. Participants will complete the Graded Symptom Checklist (GSC) prior to, immediately following, and 15 minutes following the incremental cycle ergometer test.

ACTIVE intervention. The ACTIVE training program uses exercise to expedite clinical concussion recovery, while simultaneously promoting and enhancing physiological healing. Researchers must first ensure the methodology is safe and feasible and understand how the intervention changes important clinical and physiological outcomes in healthy cohorts before implementing the protocol in concussed patients.

Healthy individuals randomized to the intervention group will be asked to exercise at their individualized target exercise intensity zone, which will progress from 60 to 80% of peak oxygen consumption (VO_{2peak}) during the maximal exercise test according to exercise guidelines set forth by the American College of Sports Medicine (ACSM). Healthy participants will exercise 3 days/week for two weeks, stopping at 30 minutes or the participant's volition. All individuals undergoing ACTIVE training will complete the GSC prior to, immediately following, and 15 minutes following each ACTIVE training session.

Symptom outcome measures. Symptoms will be monitored throughout the clinical testing battery using an objective checklist commonly used to track concussive symptoms. The GSC lists 27 common concussive symptoms for participants to rank on a Likert scale (0= not present, 1= mild to 6= severe). The GSC has previously been found to be a sensitive, valid, and reliable assessment tool.[31,32] Change in total symptom scores from the first to second clinical assessment is the primary symptom outcome (**Table 1.2**).

Table 1.2. Clinical assessments & outcomes. * Indicates lower scores are better.

Clinical Assessment Battery	
Assessment	*Outcome*
GSC	Total Symptom Score*
BESS	Total BESS Errors*
SAC	Overall SAC Score
CNS	Verbal/Visual Memory, Psychomotor/Motor Speed, Reaction Time, Complex/Simple Attention, Cognitive Flexibility, Executive Function, Reasoning
VOMS	Near-Point Convergence

Neurocognitive outcome measures. Neurocognitive outcome measures will be assessed using a computerized testing battery (CNS Vital Signs; Morrisville, NC) and a paper and pencil mental status evaluation. The computerized neurocognitive test (CNS) is a 30-minute assessment used to evaluate an athlete's attention span, working memory, response variability, problem solving, and reaction time. CNS utilizes stimuli randomization when possible to reduce practice effects and on-screen instructions and short practice orientations are provided. We have experience using CNS,[33-36] which is reliable over time.[33] The primary outcomes for CNS are standardized scores for all calculated cognitive domains. Mental status will be evaluated using the Standardize Assessment of Concussion (SAC). The SAC is a five-minute sideline evaluation that tests an individual's orientation, immediate and delayed memory, and concentration. The SAC has been studied extensively in both healthy and concussed populations and has been proven a reliable[37,38] and sensitive[39] tool. The overall SAC score is the outcome of interest for the SAC (**Table 1.2**).

Balance outcomes measures. The Balance Error Scoring System (BESS) will be used to assess postural control. The BESS is scored by adding errors committed (**Figure 1.4**). The BESS has high intra-tester reliability (ICC=0.87-0.98)[38] and is used extensively in collegiate populations.[40-42] The primary outcome for the BESS is total errors committed during the clinical assessment battery (**Table 1.2**).

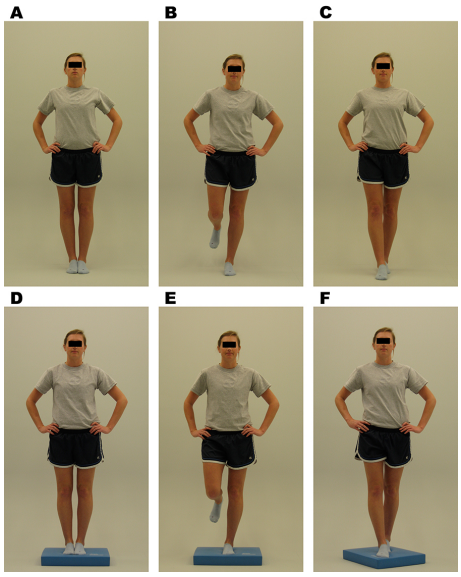


Figure 1.4. BESS uses three stances (2-leg, 1-leg, tandem) over two support conditions (firm and foam). Each 20-sec trial is done with eyes closed. Errors include: a) removing hands from hips, b) opening eyes, c) step, stumble, fall, d) hip abduction/flexion >30°, e) lifting the forefoot/heel off the testing surface, and f) out of position >5 seconds.

Visual outcome measures. The Vestibular/ Ocular Motor Screening (VOMS) is a five-

minute visual assessment that can be completed on the sideline or in clinical settings. The VOMS evaluates saccade, pursuit, convergence, vestibulo-ocular reflex, and visual motion sensitivity domains. Participants are asked to self-report four symptoms (headache, nausea, dizziness, and fogginess) prior to and immediately following assessment in each visual domain. An increase in symptom score of >2 points following a visual test is indicative of concussive injury.[43] The VOMS is sensitive to concussion.[43] Near-point convergence distance is the visual outcome of interest in this study (**Table 1.2**).

C2) Aim 2. To test the hypothesis that healthy college-aged participants randomized to ACTIVE training will have significantly improved resting-state EEG and cardiopulmonary outcomes compared to healthy college-aged participants in the control group. *Participants will complete two, identical physiological assessment consisting of a maximal exercise test and rs-EEG evaluation. Healthy participants randomized into ACTIVE training will perform 6 training sessions over a 10- to 14-day period between physiological assessments. The control group will complete the second assessment along the same 10- to 14-day timeline with no intervention between assessments. We hypothesize that healthy participants randomized to ACTIVE training will have significantly better rs-EEG and cardiopulmonary outcomes compared to healthy participants in the control group.*

C2a) Physiological outcomes and exercise. In healthy populations, changes in EEG frequency variables, particularly power, occur during exercise and persist for approximately 10 minutes following the cessation of activity.[44,45] No differences in rs-EEG variables exist between hemispheres during exercise and it is theorized that change are driven by peripheral, not neural, factors.[44] Long-term aerobic training alters rs-EEG outcomes during resting-state conditions in pathologic populations, but has not been studied in healthy participants.[29] Aerobic training enhances a number of cardiopulmonary outcomes including VO_{2max}, respiratory exchange ratio, and ventilatory threshold.[19] It is known that the frequency, duration, and intensity of the training

influences the amount of change in these outcomes,[46] but an optimal duration of exercise has yet to be established. It is traditionally recommended that exercise interventions are at least 8 weeks in length, but studies have found large (>10%) increases in VO_{2max} following only three weeks of training.[47]

C2b) The maximal exercise test and the cycle ergometer described in **C1b** will be utilized in this aim in the identical fashion as described in *Aim 1*. Additional assessments and outcomes related to *Aim 2* are described below.

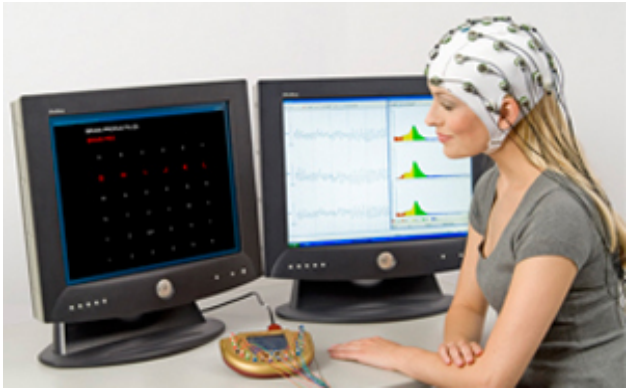


Figure 1.5. Brain Products EEG system that will be used to collect resting-state EEG data.

Resting-state EEG markers of neurological function. A portable Brain Products (Munich, Germany) EEG System, including a 16-channel actiCAP with integrated noise subtraction circuits and BrainVision V-Amp, will be used to collect resting-state EEG during four, two-minute blocks: eyes open sitting, eyes open standing, eyes closed sitting, and eyes closed standing (**Figure 1.5**). Data will be collected in a dark, quiet room using BrainVision Recorder Software on a research laptop dedicated for EEG use. Resting-state EEG will be pre-processed to remove artifacts and subjected to a Fast Fourier Transform (FFT) to obtain spectral outcomes of interest (**Table 1.3**): mean power across all bandwidths, peak alpha power, alpha/theta ratio, and left-right asymmetry in frontal, central, and posterior regions-of-interest. Resting-state EEG has previously been shown to be a valid physiological measure,[48] highly reliable over time,[49] and sensitive to concussive deficits.[48,50,51]

Table 1.3. Physiological assessments & outcomes.

Physiology Assessment Battery	
Assessment	*Outcome*
rs-EEG	Mean power Peak alpha Alpha/theta ratio Left/right asymmetry
Metabolic Cart	VO_{2max} Respiratory exchange ratio Ventilatory threshold

Cardiopulmonary measures of fitness. A ParvoMedics TrueOne® 2400 metabolic cart

will be used to measure cardiopulmonary variables. Participants will wear a noseclip and breathe through a mouthpiece attached to a Hans Rudolph 2700-series non-rebreathing valve that is held by a Hans Rudolph 2726 head-support during each incremental cycle ergometer session. The metabolic cart will calibrated according to the manufacturer's instructions prior to each data collection session. The ParvoMedics TrueOne® 2400 Metabolic cart has been shown accurate and reliable over time.[52,53] The metabolic cart reports 5-second averages of all data. The average of the three highest oxygen uptakes, respiratory exchange ratios, and ventilatory thresholds will be used in this study (**Table 1.3**).

C3) Aim 3. To test the hypothesis that ACTIVE training is safe and feasible in college-aged participants. *Investigators will evaluate the feasibility of ACTIVE training by examining the eligibility, enrollment, and retention rates of participants, effectiveness of randomization procedures, potential for contamination, number and reasons for missed sessions, and methodological barriers. (Forms listed below are added as an appendix to this document) We hypothesize that ACTIVE training will be a feasible intervention for healthy college-aged participants.*

C3a) Safety and feasibility of concussion rehabilitation. No researchers utilizing exercise as rehabilitation in concussed populations have first reported the feasibility of the intervention in healthy populations although this is considered best practice.[54] It is difficult to discern the true feasibility and effectiveness of these rehabilitation interventions without understanding the degree of change expected in healthy individuals. A number of non-exercise related concussion rehabilitation paradigms have been evaluated in healthy populations[34,55] and have been shown to be feasible. However, the lack of exercise components makes it difficult to draw comparisons to the proposed study. Exercise has been shown as safe in both healthy[56] and concussed participants[57,58] without cardiovascular risk factors, although the majority of concussed patients evaluated are in chronic recovery stages with little known about the safety

of exercise acutely following injury.

Table 1.4. Feasibility outcomes of interest for the current study. Assessment tools to obtain each feasibility outcome and time at which the outcome measure is collected are listed.

Feasibility Outcome Measures	How its assessed	When the measure is collected
Percent of individuals who met inclusion criteria	**Screening Log.** A standardized log will be kept to screen all patients for study participation. All individuals contacted by the research team will be screened for inclusion and enrollment will be tracked.	At initial clinical visit
Percent of eligible participants who enroll into the study		
Perceived difficulty	**Borg RPE Scale**. The Borg Scale is a valid and reliable measure of rate of perceived exertion[59,60]. Participants will rate exertion on a scale from 6 (no exertion at all) to 20 (maximal exertion).	During every ACTIVE training session
Number of sessions ended early	**ACTIVE Training Log.** The ACTIVE training log documents information about the intervention protocol and will be collected at every intervention session. Target exercise intensity for the session, heart rate at beginning and end of the intervention, time and reason of session termination if ended early, potential adverse events, and missed intervention sessions and reasons will be tracked on this document.	
Number of adverse events		
Average change in HR/RPE during a session		
Reasons for missed session		
Percent of sample who begin intervention on time		
Percent retained throughout the study		
Enjoyment of intervention	**Satisfaction Surveys**. Following study termination, participants in the intervention group will complete a custom eight-question satisfaction survey. Participants will be asked to rate from 0 (strongly disagree) to 4 (strongly agree) questions surrounding their overall enjoyment and satisfaction of the intervention, as well as if they perceived the intervention to be useful and convenient.	At the end of participation
Convenience of intervention		
Percent of complete data	**Study Dataset**. Percent of complete data will be evaluated from the study dataset and comparisons between the intervention and control groups will be made on any potential covariate to assess equivalence between randomization arms.	End of data collection
Effectiveness of Randomization Procedure		
Level of contamination	**Physical Activity Tracking**. Participants will be equipped with Fitbit Charge HR monitors (San Francisco, CA) to track physical activity throughout the day.	Daily

C3b) ACTIVE training is described above (**C1b**). The measurement tools and outcomes used to assess the safety and feasibility of ACTIVE training and the study methods and procedures are described below (**Table 1.4**).

C4) Expected outcomes, potential problems, alternative solutions for Aims 1-3. We expect ACTIVE training to be a safe and feasible intervention in healthy college-aged participants. In addition, we expect ACTIVE training to increase most clinical and physiological outcomes. Ensuring the safety and feasibility of the intervention in healthy participants is a

necessary first step to implementing ACTIVE training into a concussed population. *If ACTIVE training can improve outcomes on clinical concussion assessment tools in healthy participants, this will provide support for the rationale of exercise as rehabilitation as a means to improve the most common deficits seen following concussion.* In addition, an improvement in clinical outcomes following improvements in aerobic exercise training would have high clinical relevance, as directly comparing baseline to post-injury measures can lead to inappropriate decisions regarding diagnosis and can unintentionally jeopardize athlete safety. If the intervention group displays improvements in EEG and physiological variables, this would provide support that ACTIVE training improves the underlying physiological and neurophysiological deficits driving clinical change. *Future R studies (e.g., R03, R21, or R01) can more thoroughly study the link between physiological variables, clinical outcomes, and recovery, which may elucidate potential biomarkers for diagnosis and recovery as well as other therapeutic interventions that can target the physiological deficits following concussion.* Although we hypothesize ACTIVE training to be a safe, feasible, and appropriate intervention to enhance clinical and physiological measures, the duration of the intervention may not be long enough to see the expected changes. Identifying potential barriers to the implementation of ACTIVE training is an important finding and would allow us to develop strategies to circumvent these issues. This ensures that positive or negative findings regarding the effectiveness of ACTIVE training in a concussed sample in future studies are the true result of the intervention and not due to extraneous, yet controllable, factors. Finding no significant improvements on clinical measures would ensure clinicians are using the most appropriate methods to diagnose and manage concussions on the sidelines. If rs-EEG or blood biomarker outcomes do not change following physical activity, it may provide evidence that the stability of these tools increase their appropriateness as a diagnostic and management tool if appropriate biomarkers of injury are discovered.

——————————PILOT STUDY: CONCUSSED PARTICIPANTS——————————

D) SIGNIFICANCE

There is a growing body of literature suggesting physiological disturbances following concussion, which consistently persist beyond clinical resolution.[61-63] Current concussion management guidelines suggest physical rest until asymptomatic[21,64] despite the fact that aerobic exercise may improve the physiological disturbances affected by concussion, including cerebral metabolism and blood flow[61] and sympathetic nervous system activity.[65] Aerobic exercise following concussion also has high clinical utility of aerobic exercise, with studies finding that individuals engaged in physical activity have reduced symptom burden,[6,66,67] increased cognition,[68] and decreased depression scores[68] compared to individuals undergoing rest following injury. While the literature surrounding this topic is small but largely in agreement about the benefit of exercise, these studies are generally completed in participants in chronic recovery stages and are limited by a number of factors including the failure to assess physiological changes or adaptations resulting from the aerobic training. *The contribution of the proposed research is significant because it will identify the effectiveness of an acutely implemented active rehabilitation program in improving clinical and physiological outcomes in concussed college-aged participants*. We believe our intervention will be effective in shortening symptom duration and return to unrestricted athletic participation in concussed participants by improving clinical and physiological variables. This holds the potential to mitigate prolonged recovery and minimize or eliminate the deleterious consequences associated with concussion. *This research has the potential to significantly alter current clinical concussion management, which advocates solely for complete cognitive and physical rest until asymptomatic*. In addition, a feasible, clinician-friendly rehabilitation intervention can circumvent the need for individuals to be assessed by multiple specialists, such as vestibular therapists, optometrists, and neuropsychologists, which can significantly reduce the human and financial burden associated with post-concussion care. *In the future, this line of research can be extended to future R01*

prospective studies that identify the optimal dosage and timing of active rehabilitation strategies to maximize clinical and physiological recovery.

E) INNOVATION

The major governing bodies in concussion diagnosis and management currently advocate for complete physical and cognitive rest until asymptomatic, followed by a clinical evaluation in conjunction with symptom reporting, neuropsychological testing, and motor control assessments before returning athletes to play.[64] Consensus statements provide clinicians with little to no specific guidelines on if, when, and what types of rehabilitation to implement for athletes who are slow to recover. These expert guidelines, considered the gold standard in concussion management, fail to suggest safe and feasible rehabilitation protocols that can be used to expedite all aspects of recovery. In addition, physiological components of injury and recovery remain largely unstudied, leaving return to play decisions highly subjective. *The proposed study is innovative because it provides a detailed, active rehabilitation protocol that can be applied acutely in the recovery process and includes objective, physiological outcomes.*

ACTIVE training is implemented at a novel time (acute stage) in the recovery process. Multiple studies show that exercising concussed individuals below their symptom threshold can expedite symptom resolution[5-8] and decrease depression scores.[8] Exercise as rehabilitation may be especially beneficial for athletes, as they reach clinical recovery three times faster than non-athletes.[6] Current clinical guidelines advocate for complete cognitive and physical rest until asymptomatic[64,69] even though the *best evidence*

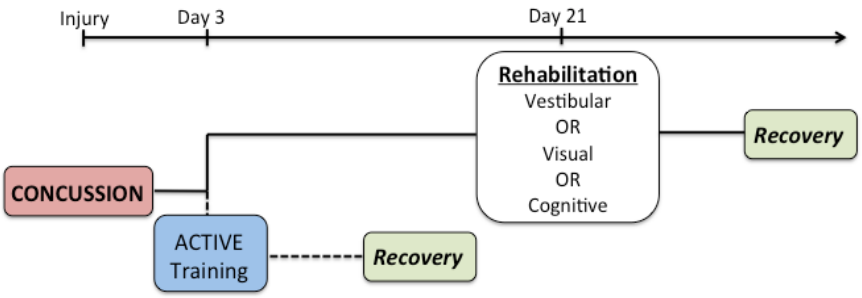


Figure 1.6. ACTIVE training is innovatively targets clinical and physiological domains affected following concussion, which may shorten recovery times.

currently available suggests only three days of complete rest followed by activity as tolerated.[2] Exercise training as concussion rehabilitation has only been implemented in chronic (3+ weeks) recovery stages[5-8] (**Figure 1.6**).

The effectiveness of ACTIVE training in improving physiological measures, in addition to traditional clinical outcomes, will be investigated. The major governing bodies in sport concussion currently advocate for a multi-faceted battery of assessments in diagnosis and management.[64,69] However, *these tools fail to include a physiological component of recovery, negating to address this aspect, and subsequent recovery, of injury*. The need for an objective tool to evaluate physiological changes and recovery following concussion is paramount as up to 53% of high school[70] and 80% of collegiate[17] athletes attempt to underreport injury. This proposal is innovative because it seeks to establish how exercise as concussion rehabilitation influences physiological measures over the course of clinical recovery. This data obtained from this study may serve as pilot data for future studies investigating novel biomarkers for concussion diagnosis, management, and return to play decisions.

F) APPROACH FOR EXPLORATORY AIMS

Concussed individuals will be recruited from the same resources as healthy participants and randomized into ACTIVE training (intervention) or control (no intervention) groups. Procedures will be identical to those in healthy participants with the following exceptions. Concussed participants will undergo the same clinical and physiological assessment batteries as the healthy participants; however, concussed participants will complete each assessment battery along relevant clinical timelines (within three to seven days following injury and after 24 consecutive hours without concussive symptoms). Concussed participants randomized into the intervention group will complete ACTIVE training at least 3 days a week until they become asymptomatic, while the control group will follow physician's guidelines for recovery (current clinical standard of care). Study participation will terminate following clearance for full athletic

return by the physician and/or athletic trainer (**Figure 1.7**). Our *central hypothesis* is that acutely concussed college-aged participants randomized to ACTIVE training will significantly improve on clinical and psychological outcomes compared to individuals randomized to the control group (Aims 1 & 2) and that this intervention will be feasible (Aim 3).

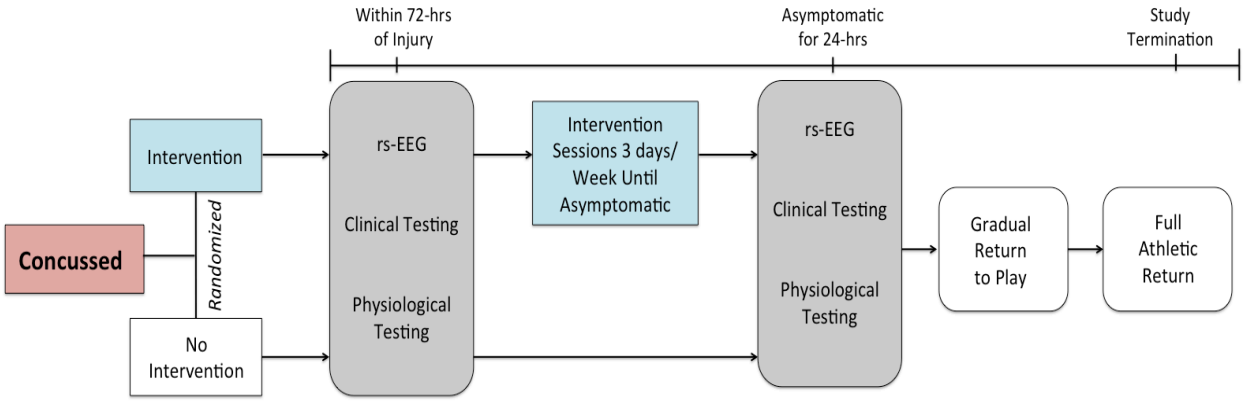


Figure 1.7. Concussed participants will be randomized to ACTIVE training (intervention) or control (no intervention) groups. Each group will complete identical clinical and physiological assessments batteries within 3-7 days of injury and when asymptomatic for 24 hours. The intervention group will complete intervention sessions three days per week until they reach asymptomatic status.

Recruitment and consent. A research team member will communicate with UNC's Sports Medicine staff daily to identify potential concussed participants. A research team member will approach individuals in a clinical setting (athletic training room or sports medicine office) to screen for eligibility. Individuals interesting in participating will sign appropriate consent forms during this initial meeting and will be randomized to the intervention or control group upon consent. We have years of experiencing working with concussed college students and have successfully recruited over 70% of eligible concussed participants for studies using similar assessments. Our research team has never had an adverse event working with concussed participants.

Operational definitions of concussion, asymptomatic, and recovery. This study adheres to the UNC Concussion Management protocol for the study definition of concussion, asymptomatic, and full recovery in order to obtain the most clinically relevant outcomes.

Concussion will be defined as a transient impairment of mental functions such as memory, balance/equilibrium, and/or vision as a result of a direct or indirect blow to the head. A physician or athletic trainer must diagnose a concussion using this definition in order for a patient to be eligible to participate in this study. Concussed participants will be deemed asymptomatic when their symptoms have returned to pre-injury levels for 24 consecutive hours. A participant will be recovered from their concussion when they have successfully completed a progressive return to play protocol and have been cleared for full sport participation by their physician and athletic trainer.

F1) Exploratory Aim 1: To determine differences in clinical outcomes in acutely concussed college-aged participants randomized to ACTIVE training compared to acutely concussed college-aged participants randomized to the control group. *Concussed participants will complete the same clinical assessment battery as healthy participants. Concussed participants will complete assessments within 3-7 days of injury and following 24 consecutive hours without concussive symptoms. The intervention group will complete sub-symptom exercise training at least 3 days per week until their symptoms resolve. Participants randomized to the control group will follow their physician's guidelines for rest and recovery. All concussed participants will be followed until their physician and/or athletic trainer clears them for full athletic participation. We hypothesize that acutely concussed participants randomized to sub-symptom exercise training will significantly improve on all clinical assessment outcomes, with the exception of near-point convergence, and will be asymptomatic and recovered sooner than concussed participants randomized to the control group.*

F1a) Current exercise rehabilitation paradigms. Sub-symptom exercise as concussion rehabilitation is used extensively in patients with PCS.[5,6,14,68,71] Patients who complete exercise show a reduction in concussive symptoms,[6] return to pre-injury activities,[6,68,71] and have improved cognitive scores.[68] Exercise as rehab has a large, positive

effect on patients (***d***=2.50) and appears to be increasingly beneficial for athletes, as they recover three times faster using exercise than concussed non-athletes.[6] One study by has investigated the effectiveness of exercise as treatment in "relatively early" stages of recovery.[58] Researchers found no differences in recovery times between the exercise and no-exercise group. However, critical methodological flaws limit this study including: failure to detail when the intervention was implemented, lack of control in the exercise intervention (intensity of exercise based on subjective rate of perceived exertion only), and a small sample size. Moderate, not vigorous, physical activity is safe when applied acutely after concussion.[58]

F1b) The intervention, assessments, and outcome measures are identical to those in *Aim 1* (**C1b**) with the following exceptions:

Maximal exercise test protocol. The timing and intensity of the maximal exercise test protocol is more mild than those completed by healthy participants (**C1b)** to enhance protocol safety and reduce the risk of potential adverse responses to exercise. Participants will start cycling at 0W and workload will increase by 25W during each stage throughout the protocol. Stages last for three minutes during the first 15 minutes of the protocol then advance every minute following. Concussed participants will be instructed to terminate the maximal exercise test immediately if any of their concussive symptoms are exacerbated by exercise or if any new symptoms present. Participants will continue until volitional fatigue if no exacerbation of current symptoms or no new symptoms are reported (**Table 1.5**).

Table 1.5. Maximal exercise test protocol for concussed participants. Workload (watts) at protocol termination will determine individualized exercise intensity for ACTIVE training sessions.

Maximal Exercise Test
0:00- Begin pedaling at 0W workload
3:00- Workload increased to 25W
6:00- Workload increased to 50W
9:00- Workload increased to 75W
12:00- Workload increased to 100W
15:00- Workload increased to 125W
Every minute following, workload increased by 150W
Termination- Symptom exacerbation, presence of new symptoms, or volitional fatigue

ACTIVE intervention. Concussed participants will complete ACTIVE training at least for 3 days a week at a level below their symptom threshold, stopping at 30 minutes of physical

activity or the first sign of symptom exacerbation. Exercise intensity will be progressed throughout the training following ACSM guidelines as tolerated by the participant; however, exercise training will be reduced or even interrupted at any sign of worsening concussion symptoms. The ACTIVE training will terminate when participants are defined as asymptomatic.

Adverse event protocol for concussed participants. A protocol has been established to appropriately address any potential adverse events. Concussed participants will be monitored following each exercise session. If the patient is still experiencing increased symptoms (compared to their pre-exercise symptom reporting) for 30 minutes following exercise, the certified athletic trainer on site will evaluate the participant to determine if medical intervention is required. If the participant is still experiencing increased symptoms 24 hours following an ACTIVE training session, they will be scheduled for a follow-up appointment with their physician. In the case of other of adverse events (falling off the cycle ergometer, passing out, etc.), participants will be seen immediately by the certified athletic trainer on site, who will recommend appropriate care in consulting with the patient's physician. It will be up to the physician and participant if they wish to continue with the ACTIVE training protocol following an adverse event. A similar adverse event protocol has previously been used in a concussed population.[72]

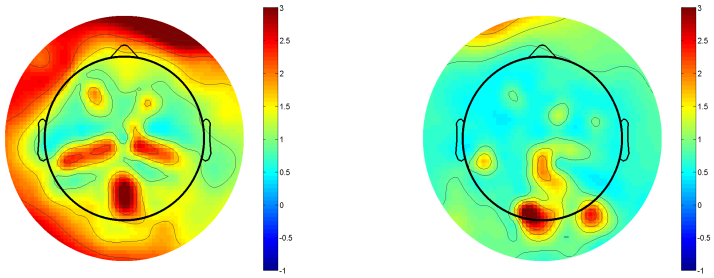
Asymptomatic and recovery outcome measures. Concussed participants will continue to be monitored following their second assessment battery in order to determine duration from injury to important clinical time points. The primary outcome measure is the time (in days) from concussion to asymptomatic and from injury to full athletic participation.

F2) Exploratory Aim 2. To determine changes in physiological outcomes in acutely concussed college-aged participants randomized to ACTIVE training compared to acutely concussed college-aged participants randomized to the control group. *Concussed participants will complete two, identical physiological assessment consisting of a maximal*

exercise test and rs-EEG evaluation. Concussed participants will complete these evaluations within three to seven days following injury and the assessment battery will be repeated when participants are deemed to be asymptomatic. We hypothesize that acutely concussed participants randomized to ACTIVE training will have significantly better rs-EEG (increased mean power, peak alpha, and alpha/theta ratio and decreased asymmetry) and cardiopulmonary outcomes (increased peak oxygen consumption, increased ventilatory threshold, and lowered respiratory exchange ratio) than acutely concussed individuals randomized to the control group.

F2a) Physiological changes following concussion. One study has examined the relationship between exercise and EEG variables in recently concussed, but asymptomatic, college athletes. Frontal alpha power and whole brain theta and delta power were increased during an exercise session. Central and posterior power in all bandwidths were increased immediately following exercise relative to pre-exercise values in both healthy and concussed athletes, with significantly larger increases in the concussed group.[45] No studies have evaluated the influence of an exercise-training program on rs-EEG outcomes. Physiological outcomes of interest have been widely studied follow exercise interventions in healthy individuals, but the recommendations for physical rest have precluded researchers from examining these variables in concussed participants. To our best knowledge, this is the first study to evaluate changes in cardiopulmonary outcomes following exercise training in acutely concussed participants.

Figure 1.8. Visual representation of alpha power during the eyes open standing condition at baseline (left) and post-concussion (right).



F2b) Pilot Data. Our preliminary data suggests that collegiate athletes (n=8) have reduced spectral power

following concussion compared to pre-injury levels, particularly in frontal and posterior regions in the alpha bandwidth (**Figure 1.8, Table 1.6**). This is in agreement with other studies[73-75] that have found spectral measures of EEG to be altered for days to weeks following injury, suggesting neuronal dysfunction or reduced integrity of thalamo-cortical circuits after concussion.[76] However, nearly all of these studies are cross-sectional. What remains unknown is if, and how, these neurophysiological variables change over the course of clinical recovery and if active rehabilitation differentially affects these outcomes.

Table 1.6. Power values over regions of interest in the alpha band found in the preliminary study. All value were statistically significant at the p<0.05 level.

Condition	Region of Interest	Mean Alpha Power over Region	
		Baseline	*Concussion*
Eyes Closed Sit	Frontal	1.46	0.70
	Posterior	1.97	0.87
Eyes Closed Stand	Frontal	1.65	0.82
	Posterior	2.29	0.93
Eyes Open Sit	Frontal	1.26	0.67
	Posterior	1.52	0.77
Eyes Open Stand	Frontal	1.57	0.68

F2c) The maximal exercise test protocol and ACTIVE intervention sessions for the concussed individuals will be completed with modifications described in *Exploratory Aim 1* (**F1b**). The EEG and metabolic cart (**Figure 1.9**) described in Aim 2 will be used for this aim with the same outcomes of interest.

Figure 1.9. The metabolic cart that will be used to measure cardiopulmonary variables throughout this study.

F3) Exploratory Aim 3. To evaluate the feasibility of implementing ACTIVE training to acutely concussed college-aged participants. *Investigators will evaluate the feasibility of ACTIVE training in concussed individuals by examining the eligibility and retention rates of participants, effectiveness of randomization, potential for contamination, satisfaction of participants, and*

methodological barriers. We hypothesize that ACTIVE training will be a feasible intervention for healthy college-aged participants.

F3a) Feasibility of concussion rehabilitation. One study has investigated the feasibility of exercise applied acutely after concussion;[58] however, there is a lack of clarity surrounding the methodology. The authors state that the first evaluation following concussion occurred two days (median) following injury and athletic trainers met with athletes daily, but no information regarding which day the intervention started or the number of training sessions per week was explicitly stated. In addition, exercise intensity was based on a subjective self-report of perceived exertion. Regardless, the authors report a low recruitment (18%) but high retention (92%) rate. In addition, the fidelity of the study was excellent, with 93% of the exercise sessions occurring at the proper intensity and only 10% of sessions terminated early due to symptom exacerbation. Recruitment rates are higher in studies with PCS populations (33%), while retention rates are approximately the same (91%).[6]

F3b) The approach to evaluating the feasibility of implementing ACTIVE training in concussed participants is identical to those in healthy participants and are outlined in Aim 3 (**C3b**). All of the assessments and related outcomes utilized in this aim are described in **Table 1.4**.

F4) Expected outcomes, potential problems, alternative solutions. We expect ACTIVE training to be a safe and feasible intervention in acutely concussed participants, improve clinical and physiological outcomes, and shorten recovery time compared to the control group. *Expediting clinical recovery has numerous positive benefits to concussed populations including diminished academic and psychosocial consequences,[3,4] reduced physical de-conditioning,[2] and decreased economic and time burdens related to multiple physician visits*. Shortening clinical recovery may be advantageous, but doing so without proportionally enhancing physiological recovery may jeopardize player safety by returning athletes to the

playing field faster while leaving their brain in a more vulnerable state to subsequent injury. We expect that ACTIVE training will address the specific pathophysiological deficits associated with concussion and expedite physiological markers of recovery. *The effect of enhanced rs-EEG outcomes can have important clinical outcomes, including reduced risk of subsequent concussion, associated co-morbidities, and late-life consequences of repetitive head trauma that can be addressed in future, longitudinal R01 studies.* ACTIVE training is anticipated to be a feasible and effective intervention, but a number of valuable outcomes can be gathered if our hypotheses are not supported. Identifying barriers to the feasibility of the intervention procedures and protocol is necessary to modify the intervention. Modifying the intervention, if necessary, will help create the most effective and practical intervention. The intensity of ACTIVE training sessions for concussed participants is designed to be conservative in order to emphasize participant safety. However, participants may need to terminate intervention sessions early due to symptom exacerbation. A similar study has found this to be a minor occurrence[58] (10% of exercise sessions stopped early) and symptoms typically improve for concussed participants within 24-hours following physical activity.[72] Participant's response to exercise will be evaluated by an independent medical monitor and adjustments to the exercise protocol will made as needed to prioritize participant safety. There may be minor discrepancies between when a clinician feels an athlete can be appropriately returned to play and can potentially affect the time to full athletic return time point. This is unlikely to significantly affect results due to UNC's policy surrounding concussion management.

————————————OVERALL ANALYSIS, SUMMARY, AND TIMELINE————————————

G) Power and analysis plan. Adequate sample size is estimated with an a priori power analysis (G*Power Version 3.1, Düsseldorf, Germany). The lowest correlation among repeated measures for all outcomes collected during this study was used to ensure all outcomes were appropriately powered. Assuming a medium effect size, alpha= 0.05, power= 0.80, number of groups/time points= 2, and correlation among repeated measures= 0.49, the number of

participants needed to adequately power all primary outcomes of interest is 36 (18 per group). We aim to enroll 40 healthy participants (20 intervention, 20 control) to allow for possible attrition. Recruitment for concussed participants is constrained by injury diagnosis and we will recruit as many eligible participants as possible during the data collection period. Mixed-model ANOVAs will evaluate potential differences in clinical and physiological outcomes between intervention and control groups for both healthy and concussed participants (**Table 1.7**). Kaplan-Meier curves with log-rank tests of significance and Cox Proportional Hazard Models will additionally be used to evaluate recovery time for concussed participants. Feasibility outcomes (**Table 1.4**) will be analyzed using a combination of descriptive statistics and qualitative analyses.

Table 1.7. Proposed statistical analyses for all study aims.

Research Question	Variables		Statistical Analysis
	Independent	Dependent	
Aim 1. To determine differences in clinical outcomes in healthy participants in ACTIVE and control groups	Clinical Assessments (2); Group (2)	GSC Total Symptom Score, SAC Total Score, BESS Total Score, NPC Distance, CNS Domain Scores	Mixed Model ANOVA
Aim 2. To determine differences in physiological outcomes in healthy participants in ACTIVE and control groups	Physiological Assessments (2); Group (2)	Peak alpha, Alpha/theta ratio, Mean power, Left/right asymmetry, Peak oxygen consumption, Respiratory exchange ratio, Ventilatory threshold	Mixed Model ANOVA
Aim 3. To evaluate the feasibility of ACTIVE training in healthy participants	Feasibility outcomes in healthy individuals	See **Table 4**	Descriptive Statistics; Qualitative Analysis
Exploratory Aim 1. To determine differences in clinical outcomes in concussed individuals in ACTIVE and control groups	Clinical Assessments (2); Group (2)	GSC Total Symptom Score, SAC Total Score, BESS Total Score, NPC Distance, CNS Domain Scores	Mixed Model ANOVA
		Days to asymptomatic* Days to recovery*	Kaplan-Meier curves; Cox Proportional Hazard Model
Exploratory Aim 2. To determine differences in physiological outcomes in concussed participants in ACTIVE and control groups	Physiological Assessments (2); Group (2)	Peak alpha, Alpha/theta ratio, Mean power, Left/right asymmetry, Peak oxygen consumption, Respiratory exchange ratio, Ventilatory threshold	Mixed Model ANOVA
Exploratory Aim 3. To evaluate the feasibility of ACTIVE training in concussed participants	Feasibility outcomes in concussed individuals	See **Table 4**	Descriptive Statistics; Independent Samples T-Test, Chi-Square

G) Overall summary and conclusions. Emerging evidence suggests three days of

complete rest followed by activity as tolerated is beneficial to concussion recovery,[12] which conflicts with clinical recommendation for complete rest until symptoms resolve.[21] Prospective studies evaluating the effectiveness of exercise as rehabilitation acutely after injury is needed to determine best practice for concussion treatment. However, researchers must vet the effectiveness and feasibility in a healthy population to ensure the intervention is feasible and targets desired outcomes prior to testing the intervention in concussed populations. In addition, researchers must explore the intervention in a concussed sample, to ensure the intervention is safe and to determine any potential barriers to effectiveness. We will understand the effectiveness of ACTIVE training in improving clinical and physiological outcomes in healthy college-aged participants and know the safety and feasibility of the intervention following the completion of this study. In addition, we will begin to understand how ACTIVE training influences recovery in acutely concussed individuals and any potential barriers specific to a concussed population. This allows us to adjust factors surrounding the intervention or study procedures to enhance the feasibility and safety of ACTIVE training. We will collect the pilot data necessary to seek future funding to determine the optimal duration, intensity, and frequency of ACTIVE training to create the largest improvements in clinical and physiological outcomes. An exercise as rehabilitation intervention applied acutely after concussion holds the potential to reduce the co-morbidities associated with concussion and risk of future injury. If exercise as rehabilitation interventions are found to positively effect concussion recovery acutely after injury, they can begin to be implemented into widespread concussive populations and become the basis for new clinical treatment recommendations for concussed individuals.

H) TIMELINE. The proposed project will take 18 months to complete and **Table 1.8** provides the timeline. The first three months of the project include personnel training and the beginning of subject recruitment and data collection. The research team has a history of recruiting and retaining over 15 healthy participants per quarter for an intervention of this

magnitude, so we are confident we will achieve our desired sample size for the primary aims. Approximately 5 UNC club sport athletes get concussed every quarter and we anticipate successfully recruiting and retaining at least 10 concussed participants for the pilot study. Data processing will be completed immediately after each subject finishes his/her participation to verify data quality and prevent long delays in analysis. The data will be disseminated through manuscript and conference presentations at the end of the study period.

Table 1.8. The proposed project will take 18-months to complete.

Task	*2016*				*2017*	
	Q1	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*
Personnel Training						
Subject Recruitment						
Data Collection						
Data Processing						
Data Analysis						
Manuscript Preparation						

CHAPTER 2

LITERATURE REVIEW

Every year, 500,000 concussed individuals suffer from prolonged recovery.[10] Concussed individuals typically recover within 7-10 days, but a small yet significant subset suffer with symptoms and objective deficits for weeks to months after injury.[21] Prolonged recovery can morph into Post-Concussion Syndrome (PCS) without resolution of concussive deficits. Post-Concussion Syndrome is the leading cause of concussion-related disability[10] and leads to negative cognitive,[3,77,78] academic,[3,4] psychsocial,[3] and emotional[79] deficits.

Current best practice advocates for complete cognitive and physical rest until a patient becomes asymptomatic.[21,64] Although the mechanism behind and factors contributing to prolonged recovery are relatively unknown, active treatments are available for individuals who are slow to recover with rest alone.[13] Vestibular,[80,81] visual,[82-84] and multi-modal[68,71] rehabilitation are effective treatments, but sub-symptom exercise as rehabilitation[5,6,14] shows the most promising results in individuals with PCS. However, rehabilitation is often not prescribed for three or more weeks following injury due to the recommendations for complete cognitive and physical rest,[68,71,81] forcing patients to suffer with significant deficits for relatively long amounts of time.

Current literature does not support the recommendation of prolonged rest and suggests three days of rest followed by activity as tolerated as optimal treatment.[12] Sub-symptom exercise is a promising treatment in PCS populations; however, the effectiveness of this therapy on clinical and physiological outcomes when applied in acute recovery stages remains

unknown. Understanding the effect of sub-symptom exercise in the acute phase of injury may have substantial benefits including the ability to expedite recovery and reduce the risk persistent concussive deficits.

Concussion

Concussions have been identified as a major public health concern and concussion research is considered a high priority in the injury prevention literature.[85] There is no universally agreed upon definition for concussion, but the International Conference on Concussion in Sport Group defines concussion as "a complex pathophysiological process affecting the brain, induced by biomechanical forces."[21] Concussions are believed to largely reflect a functional injury, resulting in a host of subjective symptoms and objective balance and cognitive deficits.[21] As such, concussion is ultimately a clinical diagnosis based off a structured evaluation completed by an experienced medical provider, with supporting objective evidence.

The Physiological Consequences of Concussion

Standard neuroimaging rarely reveals abnormal findings after concussion, suggesting that concussive symptoms are the result neuronal dysfunction.[86] Recent research has highlighted several physiological disruptions that often persist beyond clinical symptoms and impairments[61,62] despite the assertion that concussions are largely a functional injury.[21] This review will focus on neurometabolic, autonomic nervous system, and cerebrovascular impairments due to their relationship with aerobic exercise.

Neurometabolic. A number of metabolic abnormalities are detected in the brain following concussion. An unsystematic amount of various neurotransmitters are released and an unregulated amount of ionic fluxes occur.[86] The sodium potassium pump is put into overdrive in an effort to restore ionic balance, resulting in additional use of adenosine triphosphate.[87,88] The uptake of adenosine triphosphate creates a dramatic shift in glucose metabolism, causing a state of hyperglycolysis,[87,88] followed by a state of depression.[87] Calcium can accumulate in the brain during the depressed metabolic state and, if left unchecked, can activate metabolic

pathways that result in cell death.[87] The neurometabolic cascade activated by concussion typically resolves within 10 days, with potassium and glutamate stabilizing within a day, calcium levels restored in 3-4 days, and glucose levels returning to pre-injury levels within 7-10 days of injury.[89] It is thought that this ongoing energy crisis and metabolic disruption leads to clinical deficits seen following concussion.

Autonomic Nervous System. Several studies have demonstrated autonomic nervous system dysfunction in acutely concussion individuals as evidenced by altered sympathetic-parasympathetic balance. The literature investigating heart rate following concussion is mixed, with some studies finding increased heart rate in concussed participants at rest and at exertion,[90,91] while other studies have shown no differences in heart rate between concussed and control subjects under differing physiological conditions.[92] Concussed subjects display significantly different heart rate variability patterns than non-concussed subjects, particularly during exercise. Concussed subjects have altered low frequency to high frequency ratios and lower R-R intervals during exercise compared to controls.[93,94] Additionally, QT variability and heart rate complexity (non-linear metric) are altered following concussion and appear to correlate with clinical recovery, as significant differences were observed 4 days following injury but were absent two weeks following injury.[92,95] Taken together, concussed athletes generally display greater sympathetic and lower parasympathetic activity compared to non-injured counterparts.[94] This altered autonomic nervous system regulation is evident throughout the traumatic brain injury spectrum, with changes proportional to injury severity and improving throughout recovery.[96] The mechanism behind autonomic system alterations are unknown, but it is postulated that traumatic brain injury damages the brain centers responsible for the control of autonomic function and/or the connections between the autonomic nervous system and the heart are uncoupled following injury.[96]

Cerebral Blood Flow. The cerebrovascular effect of concussion is an emerging field with few studies currently represented in the literature. A 2014 systematic review examining

cerebrovascular changes following concussion showed that significant alterations in concussed individuals were found in all included studies.[97] Cerebral blood flow decreases following concussion, with levels typically returning to baseline within 7-10 days following injury. [63,89] Cerebrovascular reactivity is often unaltered at rest but, when challenged with physiological stress (through exercise or breath-holding protocols), concussed individuals display deficits in middle cerebral artery velocity.[98] Additionally, PCS patients showed higher cerebral blood flow velocity and lower carbon dioxide sensitivity compared to healthy controls.[99] No differences in cerebrovascular outcomes were evidence between healthy and concussed subjects following an exercise program.[99] For concussed individuals reporting symptoms of headache and/or dizziness, changes in cerebral blood flow velocity were disproportionate to exercise intensity, suggesting that cerebrovascular dysfunction may be, at least in part, the neural mechanism underpinning clinical symptoms.[99]

Current Concussion Management

Concussion management hinges around an athlete reporting as asymptomatic, or the return of all concussion symptoms to baseline, pre-injury levels. Current consensus guidelines advocate for complete cognitive and physical rest until an individual is asymptomatic, followed by a gradual return to athletic participation.[64,100] As such, very little research is available during acute recovery stages. Vestibular, visual, and exercise rehabilitation is widely encouraged in literature in chronic recovery stages;[13] however, these recommendations are often based on anecdotal evidence and clinical experience as there are few studies to support specific rehabilitation paradigms. Additionally, current concussion rehabilitation protocols are currently limited in paradigm details, including the type, timing, and intensity of rehabilitation strategies are provided. For example, Collins[101] identified six different clinical trajectories following concussion with recommended rehabilitation strategies, but the rehabilitation strategies were vague, did not detail variations or progressions of the protocol, and are based off of clinical recommendations, not empirical evidence. More empirical evidence, in addition to expert

consensus, is needed to provide clinicians with the best evidence-based practice. This proposed rehabilitation protocol is created with insights in the latest scholarly evidence and circumvents the shortcoming of previous concussion rehabilitation studies by thoroughly describing an individualized exercise protocol implemented acutely after injury, with standardized progressions for the intensity of the program as the participant improves.

Evidence for Rest Following Concussion. Rest remains the recommended treatment following concussion even though what rest encompasses is poorly understood.[64] Empirical evidence supporting the use of strict rest as concussion treatment is mixed, but the majority of the evidence supports activity as tolerated instead of complete rest.[12,69,102-106] Complete rest has only been found to improve neurocognitive scores and decrease reported symptoms in a pediatric population treated at a specialty concussion clinic, which does not represent the target sample for this study.[102,103] Instead, both prospective studies and retrospective charts reviews evaluating a variety of age cohorts and settings (college sports medicine, concussion clinic, emergency departments) have found strict rest to increase concussion symptoms and to delay recovery.[104-107] It is necessary to guide patients towards moderate levels of activity as high levels of cognitive and physical activity do delay recovery.[58,108]

The literature on rest following concussion is summed in qualitative reviews that have concluded three days of rest is ideal, followed by activity as tolerated.[12] The literature surrounding the potential benefits or detriments of rest following concussion remains sparse, but little evidence exists to support that complete rest improves concussion outcomes. Inactivity may even precipitate or exacerbate vestibular deficits and emotional symptoms, which may contribute to prolonged recovery.[12,69] Preventing athletes from exercising may additionally lead to physical deconditioning, anxiety and stress, mild depression, social isolation, and irritability,[69,109] all of which can lengthen recovery times.

Acute ***c***oncussion ***t***herapy ***i***nter***ve***ntion (ACTIVE) training is an aerobic exercise training protocol designed to facilitate concussion recovery and the protocol, including the timing and

intensity of the training schedule, is specifically designed based off of the best available evidence currently in the literature. ACTIVE training employs three days of complete rest after concussion to follow best current evidence surrounding rest and allows for allows for the restoration of ionic concentrations in neurons, particularly potassium, calcium, and glutamate.[89] Participants will complete a maximal exercise test after this initial rest period to determine an individualized exercise intensity zone, designed to be a moderate level of exercise that occurs below the symptom exacerbation threshold.

The Rationale For Exercise Following Concussion

It has been proposed that the physiological deficits occurring as a result of concussion, including the neurometabolic, autonomic, and cerebrovascular factors, underlie the clinical symptoms and deficits reported following concussion.[65,89,96] This is supported by recovery trajectories for these domains: these physiological deficits return to pre-injury levels within 7-10 days,[89,92,95] the typical concussion recovery timeline.[21] Additionally, individuals with PCS often display lingering physiological deficits,[62,65] suggesting that delayed clinical recovery is the result of abnormal physiological function.

There are several theoretical considerations for including aerobic exercise training in concussion rehabilitation strategies. First, aerobic exercise is known to affect the physiological domain comprised following concussion, including cerebral metabolism and blood flow[61] and autonomic nervous system activity.[65] By provoking dysfunctional physiological systems in a controlled manner, the body can recognize errors and adapt to improve functioning. Additionally, aerobic exercise can reduce feeling of anxiety, depression, social isolation, and stress,[109,110] which may increase recovery times. Lastly, chronic aerobic training can improve symptom,[26,72] cognitive,[111,112] and balance outcomes,[113,114] which are the clinical domains most affected by concussion.[115]

<u>Exercise as Concussion Rehabilitation</u>. Exercise as concussion rehabilitation has been investigated in PCS populations for several years; however, few studies have evaluated the

effect of acute aerobic exercise on concussion recovery. One intervention study found no difference in recovery times between acutely exercising and non-exercising athletes,[58] while a prospective cohort study found that pediatric concussed patients partaking in early exercise showed reduced risk of PCS.[116] The studies that do investigate exercise as concussion rehabilitation, including these studies, are commonly limited by a number of critical methodological flaws including small sample size, no mention of how many days after concussion participants began physical exertion, only investigating time of recovery as an outcome, and lacking control in the exercise intervention. One study investigating the safety and feasibility of a progressive exercise test in concussed subjects reported no adverse events.[57] There is no indication in the current literature that suggests acute exercise poses a safety hazard or delays recovery for participants; however, little data is available to support this.

Exercise as rehabilitation in chronic stages of concussion recovery is better studied and has consistently shown positive findings.[5,6,14,57,66-68,71] Exercise as concussion rehabilitation significantly reduces concussion symptoms, but may not target all deficits such as visual and migraine related symptoms and dysfunction.[6] Individuals are able to achieve age-appropriate maximum heart rates during exercise and return to work, school, or athletic activity following exercise rehabilitation.[6,14,71] Athletes recovered using exercise therapy three times faster than non-athletes, indicating physical activity is an especially effective form of rehabilitation in athletic populations.[6] Differences in fMRI outcomes between a concussed and control group were significantly different prior to, but not following, an exercise intervention.[5] This data serves as preliminary evidence that exercise as rehabilitation may be effective because it targets the underlying physiological dysfunction following concussion, but caution should be maintained when interpreting this study as a small sample was used.[5]

Multi-modal rehabilitation, which combines aerobic exercise, sport-specific coordination exercise, and visualization therapies, reduces concussion-like symptoms and depression scores and improves visual motor processing speed.[68,71] While multi-modal rehabilitation displays

positive findings, these studies should be interpreted cautiously as they are limited by a lack of control group and it remains unknown how the different components of the paradigm may differentially influence the programs effectiveness.

The literature surrounding sub-symptom threshold exercise as concussion rehabilitation is small, but positive. Moderate intensity exercise is safe, reduces concussion symptoms, and improves cognitive and emotional dysfunction. Clinical recommendations for complete rest until asymptomatic have prevented exercise as rehabilitation paradigms, which are successful in chronic settings from being implemented acutely. ACTIVE training seeks to be on the forefront of the shift in best practice from passive to active concussion treatment by implementing sub-symptom threshold exercise paradigms acutely in the recovery process to promote full recovery.

Clinical Concussion Assessment Battery

Symptomology

Concussions have a larger effect on self-reported symptoms than postural or cognitive deficits.[115] A 2008 meta-analysis revealed significant effects persist 14 days following injury[115] even though symptomatic deficits are typically believed to resolve within 7 days.[21] Concussive symptoms are often grouped into symptoms affecting the somatic, cognitive, or sensory domains,[117,118] with new rehabilitation paradigms being investigated to target specific symptom clusters.[101] Somatic symptoms can include headache, nausea, or vomiting.[118,119] Symptoms affecting the cognitive system include difficultly with attention, memory recall, and mental fogginess.[120] Sensory symptoms include fatigue, drowsiness, and change in sleep patterns.[118,120] Headache, balance problems, and slow mental processing are among the most frequently reported symptoms following concussion.[121,122] Concussive symptoms are typically short-lived and resolve on their own, but a small number of individuals may experience more permanent symptoms.[21] The mechanism behind prolonged concussive recovery is relatively unknown, but factors such as initial symptom burden,[123] visual/vestibular disturbances,[124]

somatization of symptoms,[125] and being female[14,126] increase the risk of experiencing prolonged recovery.

Exercise and Concussion-like Symptoms. Non-concussed participants report significantly more concussion-like symptoms following intense, compared to moderate exercise and these symptoms persist for up to 15 minutes following activity.[25] Headache, balance problems, fatigue/low energy, and pressure in the head are the most common reported symptoms following exercise in healthy individuals.[26,27] These symptoms return to baseline within a 15-minute window following the termination of the exercise, regardless of whether a cognitive load was applied during the protocol.[27] Emotional symptoms, such as depression and irritability, significantly improve (decrease) in females following exercise, while males reported fewer issues with concentration following exercise.[26,72]

Symptom reporting for asymptomatic concussed patients or those in chronic stages of recovery has also been examined following a single session of exercise. Asymptomatic concussed participants report a significant increase in symptoms immediately following an exercise bout compared to uninjured controls that persist during a 15-minute recovery period.[127] Exertion testing in youth athletes, most of whom meet the definition of post-concussion syndrome, increases symptoms during exercise and for a 30-minutes period following activity.[72] However, exercise appears to improve concussion symptoms in chronic patients, evidenced by a decrease in symptoms relative to their pre-exercise baseline seen in over 50% of the patients by the following day after activity.[72] Participants show the biggest improvements in emotional and cognitive symptoms following aerobic training.[72]

Concussion Symptom Summary. Symptom reporting is a subjective measure and is reliant on the honesty and transparency of the affected individual. It is one of the most important outcomes following concussion, regardless of its subjective nature, as the resolution of symptoms traditionally signals clearance to begin the return-to-play progression. Concussion-like symptoms increase in both concussed and non-concussed participants following a single-

session of exercise, but aerobic training in general decreases symptoms in participants in the chronic stages of concussion recovery. Understanding the influence of ACTIVE training on concussive symptoms can have large implications on concussion management, as acute exercise bouts are known to increase concussive symptoms, while long-term aerobic training decreases concussive symptoms.

Postural Control

Postural control is defined as a person's ability to maintain postural orientation, during movement or rest, in response to perturbations caused by either internal or external sources.[128,129] Commonly referred to as balance, postural control is maintained largely thorough the integration of afferent (somatosensory, visual, and vestibular) and efferent (motor) information.[130] Experts have consistently established three levels of brain structures that assist in the maintenance postural control. The cerebrum, the highest-level of the structures, is responsible for receiving and correlating input from other brain structures to create appropriate postural responses.[43,130] The maintenance of balance was once believed to be automatic (without conscious control from the cerebrum), but dual-task paradigms that show decrements in balance with the addition of cognitive tasks have largely disproved this theory. Mid-level brain structures involved in the maintenance of balance include the sensorimotor cortex, cerebellum, parts of the basal ganglia, and some brainstem nuclei.[130] The postural reflexes, the eyes, vestibular apparatus, and proprioceptors, are organized on this level, along with the alpha motor neurons making up the efferent pathways to the muscles.[130] Lowest-level structures, including the brainstem and spinal cord, relay the specific muscle tensions and joint angles dictated by mid-level structures to the appropriate receptors.[130,131]

Postural Control following Concussion. The precise physiological cause of balance deficits following concussion remains unknown, but researchers argue that concussions may injure the brainstem's reticular cortex,[131] cause damage to the vestibular organs,[54] or disrupt the brain's ability to correctly integrate the sensory information provided by the somatosensory,

visual, and vestibular systems.[130] Balance dysfunction, regardless of the origin of deficits, remains a hallmark of concussion signs and symptoms. Nearly 77% of collegiate athletes report symptoms relating to poor balance or dizziness following concussion.[122] A percentage of these athletes may be more correctly classified as having a visual issue as dizziness is known to result from dysfunction to the vestibulo-ocular reflex (VOR) pathway.[43] Approximately 40% of individuals complain of balance-specific symptoms without the inclusion of dizziness.[117] Research shows that balance following concussion is at its worst approximately 24 hours following injury.[42] Deficits presents on clinical concussion assessments, like the Balance Error Scoring System (BESS) and the Sensory Organization Test, resolve within 3-5 days post-injury.[40,42,132] However, more dynamic balance assessments, such as virtual reality balance testing and gait analyses, show deficits up to 30 days,[133,134] calling into question the true resolution of balance dysfunction after concussion. Whether the lingering deficits identified by these more research based balance assessments have clinical significance remains unstudied.

Exercise and Postural Control. A single session of exercise is known to effect measures of postural control when assessed immediately following termination of the activity. Individuals assigned to a fatigue protocol perform significantly worse (more errors) when completing the BESS immediately following exercise.[22,28] Subsequent studies confirm poorer BESS performance following exercise, but highlight that BESS score return to baseline within 20 minutes following the activity.[22,28,135] Aerobic training, as opposed to an acute bout of exercise, has been shown to improve measures of postural control in several different pathologic populations.[113,114]

Postural Control Summary. Balance issues are one of the most prominently reported symptoms after concussion. Deficits can be measured objectively through a number of clinical and laboratory based tools, with deficits typically resolving within 3-5 days. Exercise has been shown to worsen postural control immediate following activity while chronic aerobic training improves a number of postural control outcomes. Understanding the ways in which postural

control responds to a rehabilitation paradigm is clinically relevant as athletic participation requires a high-level of static and dynamic postural control for performance and injury prevention. If ACTIVE training is found to improve postural control outcomes compared to rest, future studies can explore a possible association between postural control following concussion and the risk of subsequent musculoskeletal or cerebral injuries.

Cognition

Cognitive function is defined as higher-level brain tasks such as memory, attention, executive function, and mental speed and flexibility.[118,136,137] Cognitive function is assessed through neuropsychological tests, which along with symptom reporting and balance testing are part of the recommended clinical concussion assessment battery.[138,139] Neuropsychological tests evaluate a variety of cognitive domains, including immediate and delayed recall, attention and concentration, problem-solving abilities, visual tracking, reaction time, and speed of information processing.[136] It is important that all neuropsychological tests be relatively short, easily administered by clinicians with neuropsychology backgrounds, have solid psychometric properties, have a documented history of use with athletes, and be minimally frustrating.[136] Cognitive dysfunction is thought to resolve within 7-10 days following injury,[140] while some studies suggest small to moderate cognitive deficits persist for up to 14 days.[115] Conversely, balance deficits subside within 3-5 days[40,42] and symptoms typically resolve around 7 days following injury,[21] indicating neurocognitive deficits persist longer than symptom and balance deficits.

Cognition following Concussion. Neuropsychological tests are considered the cornerstone of concussion testing because of the information they provide the clinician.[137] Neuropsychological tests provide a quantifiable way to measure cognitive function and are considered one of the most sensitive tests in the concussion testing battery.[136,137] Concussions create moderate to large effects on neuropsychological tests, with significantly poorer cognitive performance after injury[115,140] regardless if the tests were administered via computerized or

paper and pencil versions. Domains of orientation, memory acquisition, delayed memory, and global cognitive activity are most commonly affected following concussion, with deficits at their peak 24 hours following injury.[140]

Exercise and Cognition. There literature detailing the neural adaptations underpinning the relationship between exercise and cognition continue to grow with improving neuroimaging capabilities. Aerobic exercise increases both gray and white matter volume, particularly to gray matter in the frontal lobe including the dorsal anterior cingulate cortex (ACC), supplementary motor area, middle frontal gyrus, dorsolateral region of the right inferior frontal gyrus, and the left superior temporal lobe.[141] Additionally, exercise has been shown to increase hippocampal volume[142,143] and increase cerebral blood volume[143] to the hippocampus. These brain areas are heavily tied to cognition, and are implicated in a number of top-down processing domains including memory, spatial awareness, and attention.[144] However, these effects appear particularly beneficial for aging individuals to stave off cognitive decline,[144] with changes in brain volume not seen in younger populations.[141]

The literature surrounding exercise and clinical concussion assessments is sparse. Only immediate and delayed verbal memory domains are impaired when measured via the Immediate Post-Concussion Assessment and Cognitive Testing immediately following a maximal exercise test.[23] No other changes have been reported following a session of physical activity or aerobic training on any other neurocognitive tool used in concussion assessment.[23,145] Exercise is generally beneficial to cognitive outcomes when administering global cognitive assessments (ie. not those used in clinical concussion care). A bout of moderate intensity exercise increases cognitive outcomes on traditional neurocognitive tests in young,[18] healthy adults and certain aspects of cognition and performance are enhanced in healthy adults of all ages following aerobic training.[111,112]

Cognition Summary. Moderate sessions of aerobic exercise and chronic aerobic training, as opposed to maximal exercise testing, improve various aspects of cognition. ACTIVE training,

which uses moderate sessions of physical activity as a means of concussion rehabilitation, has the potential to improve cognitive outcomes. Understanding the influence of exercise on clinical concussion measures has implications for concussion diagnosis and management, as improving cognitive outcomes may expedite recovery times and minimize academic issues.

Vision

Approximately 50% of the brain's pathways are related to vision[146] and the goal of these brain centers is to work together to create clear, singular binocular vision at all times.[147] There are many domains of vision, each with distinct neurologic pathways. Saccades, or quick movements of both eyes between two phases of fixation in the same direction, are generated from the parietal eye field (reflexively) or frontal eye field (intentionally) then sent directly to the contralateral paramedian pontine reticular formation or superior colliculus.[148] Visual pursuits, or the ability to visually track a moving object, result from the descending pathways in the tempero-parietal-occipital junction and frontal eyes fields.[148] These pathways then connect in the pons and the cerebellum, which excites the sixth cranial nerve to produce pursuit movements.[148] The VOR stabilizes images on the retina by producing eye movements in the opposite direction (at the same speed) to head movements. To create the VOR, the semicircular canal signals to the vestibular nuclei, which then excites the sixth cranial nerve.[148] Vergence is a visual domain in which the eyes move in the opposite direction to maintain fusion on objects, both near and far. While the exact anatomical pathway of this domain remains unknown, it is generally accepted that cerebro-brainstem-cerebellar pathways are involved.[148]

Vision following Concussion. Visual disturbances are reported in 47-65% of individuals following concussion,[149,150] although these reports involve blast-related concussion. Only 30% of individuals complain of visual symptoms following sport-related concussion.[117] Regardless, visual dysfunction after concussion is a relatively frequent complaint and this may be due to damage in the frontoparietal circuits and subcortical nuclei, areas that are part of several visual pathways and are particularly venerable to injury from concussion.[151] Eyes movements are

highly related to cognitive domains, such as memory and attention, which commonly show dysfunction following concussion.[148] Additionally, visual deficits often translate into reduced academic or work performance,[13] which can greatly affect quality of life for concussed individuals. Visual deficits are commonly reported in individuals with PCS[11] and deficits have been shown to persist for months to years following injury.[152,153] Clinicians may be able to mitigate the cognitive and academic consequences of visual disturbance following concussion and may potentially reduce the risk of prolonged recovery by identifying and treating visual disturbances earlier after injury.

Exercise and Vision. There are no studies in humans regarding the effect of exercise, both acute and chronic sessions, on visual outcome measures. Exercise directly benefits the central nervous system and protects against neurodegenerative disease and these benefits have been hypothesized to transfer over to retinal health. However, data only exists in animal models, leaving the effect of exercise on vision largely unknown.[154]

Vision Summary. Vision plays a large role in activities of daily living, from cognitive activities to its role in balance. Each domain of vision has its own neuroanatomical pathways, many of which are susceptible to insult following concussions. The prevalence and severity of visual dysfunction following concussion, and their relations to clinical outcomes and recovery times, remain largely unstudied despite a theoretical basis for visual dysfunction following concussion. In addition, whether these potential deficits are negatively or positively affected by exercise remains unknown. ACTIVE training will be the first study to assess the influence of a short exercise-training program on visual outcomes in a healthy and concussed population, which may help clinicians to understand the role of vision following concussion and potential therapeutic interventions to improve dysfunction.

Physiological Assessment Battery

Contemporary definitions call concussion a pathophysiological component, yet no physiological tools are currently recommended as part of the clinical concussion assessment

battery. This section, therefore, does not represent a standardized battery of physiological tools to assess concussion, but rather the rationale for the inclusion of the physiological tools proposed in this study.

Electroencephalography

Electroencephalography (EEG) was the first assessment tool capable of establishing alterations in brain functioning in traumatic brain injury populations[155] and continues to be useful in the brain injury field. EEG techniques are the most commonly used method to evaluate brain functioning, due to the relatively low cost, noninvasive and uncomplicated nature of the test, high test-retest reliability, and the long, well-document history dating back to the 1930's.[156,157]

What EEG Measures. Few people understand what an EEG measures, and what the scientific community gains from those measurements, despite EEG being a common brain assessment tool. The cerebral cortex is comprised of six distinct layers. EEGs measure the electrical current in the cerebral cortex created by the summed activity of several neurons. More specifically, post-synaptic potentials from pyramidal cells in cortical layers III and V create the wave patterns seen via EEG.[20]

Concussive episodes are often caused by acceleration/deceleration forces, which can create diffuse injury. Due to the nature of these injuries, standard structural imaging, such as magnetic resonance imaging and computerized axial tomography, are typically not able to identify abnormalities. Concussive episodes are characterized by functional deficits as opposed to the structural damage or lesions found in penetrating or severe traumatic injuries. EEGs evaluate the underlying neural processes that contribute to functional networks, making them a sensitive and appropriate tool to evaluate the effects of concussive episodes.[157]

Bandwidths. It is important to first understand the frequency bandwidths that are recognized and analyzed in EEG work. A form of time series analysis is required to produce meaningful data due to the inherently complex nature of EEG data. Spectral analyses are a method to extract meaningful data by decomposing the complex waveform into the linear sum of

more elemental waves (such as sine waves or wavelets).[158] These analyses are completed to obtain a frequency spectrum, which is one way to commonly express EEG data.[158] EEG frequency ranges are reported from 0.1-100Hz in humans,[159] although lower frequency ranges are more thoroughly studied. There are minor discrepancies in the literature surrounding frequency bandwidths. For the purpose of this literature review, when referring to a specific bandwidth, please refer to the frequency ranges found in **Table 2.1**.

Table 2.1. EEG frequency ranges for each given bandwidth.

Bandwidth Name	Frequency
Delta	.5-3.5 Hz
Theta	3.5-7.5 Hz
Alpha	7.5-12.5 Hz
Beta1	12.5-24 Hz
Beta2	24-32 Hz
Gamma	32-60 Hz

Quantitative EEG. Conventional EEGs (visual inspection of raw EEG signal) lack the sensitivity to detect changes following concussion.[160] However, more complex EEG analyses, including quantitative EEG (qEEG), may be useful to assess changes after concussion.[157] Quantitative EEG transforms raw EEG waveforms into numerical values via software-assisted data analysis. Quantitative EEG analysis is advantageous, compared to conventional analyses, because it can detect subtle differences in the waveforms not visible to the naked eye.[161] This enhances the usefulness of qEEG as an assessment tool for brain injury due to its "direct signature of neural activity" and "ideal temporal resolution."[49]

Several outcome variables can be isolated using spectral analyses (detailed above). Power is calculated as microvolts^2/cycle/second and can be described in a particular frequency bandwidth or at a single electrode channel.[158] Symmetry is found by subtracting the natural log of power on the left minus the right hemisphere.[158] Concussions are believed to affect connectivity between neurons, disrupt activation of the reticular system, or cause dysfunction in thalamocortical tracts[161] Power analyses are one of the most sensitive electrophysiological measures to detect changes after concussion because they evaluate the deficits seen in these pathways.[157,161,162]

qEEG Patterns and Concussion. Several qEEG patterns have emerged after injury, although a unique pattern of concussive injury has yet to be established. The most common qEEG findings in concussion include: 1) a decrease in peak or average power in the alpha bandwidth,[73,75,163,164] increase in average power in the theta bandwidth,[165,166] or decreased alpha-theta ratio[73] and 2) reduced alpha and beta power between frontal and occipitals regions.[167,168] More recent studies investigating qEEG during clinical concussion assessments have found hemispheric differences, with concussed patients displaying power asymmetries between left and right sides.[169-171]

Value Added of EEG. EEG has a number of clear limitations, including a lack of unique patterns specific to concussive injuries[160] and a poor understanding of upper frequency bandwidths (which may have important associations with cognition[172]). EEG has several advantages over clinical assessment tools despite its limitations. Finding objective tools capable of observing and tracking physiological deficits after concussion is of paramount importance as athletes are known to not report or underreport symptoms.[173] Compared to other neuroimaging tools, EEG is non-invasive, cheaper, and has an uncomplicated procedure.[157] The high test-retest reliability reported is better than most clinical concussion assessment tools and EEG shows no practice or learning effects. With consideration to both the benefits and the limitations, EEG can compliment, not replace, the clinical concussion battery by providing additional information that may be useful during diagnosis and recovery.

EEG and Exercise. Changes in EEG frequency variables, particularly power, occur during exercise and persist for approximately 10 minutes following the cessation of activity.[44,45] These alterations in response to exercise are not different between hemispheres and it is therefore theorized that the changes are driven by peripheral factors, such as changes in the partial pressure of carbon dioxide in the blood, instead of neural factors.[44] Long-term aerobic training alters neurophysiological outcomes during resting-state conditions in depressed patients, but has not been studied in healthy participants.[29]

EEG Summary. Most individuals are thought to "fully" recover within a few weeks following injury. However, studies supporting late-life deficits related to concussion histories have led researchers to question if there are persistent low-level abnormalities after injury. Several EEG studies show deficits in concussed participants years post-injury,[174,175] suggesting that concussion results in neurophysiological deficits which may not be transient. Identifying neurophysiological changes after concussion can have important implications for diagnosis and return to play decisions, which may be able to increase athlete safety. Investigating novel therapies, such as ACTIVE training, that may improve neurophysiological deficits seen after concussion can help promote initial recovery. Additionally, therapies targeting neurophysiological domains have the potential to reduce future injury risk and late-life injury consequences, which can be addressed in future studies.

Exercise Physiology

Exercise physiology is the investigation of short-term physiological responses to the stress of physical activity and the physiological adaptations to repeated bouts of physical activity over time. Areas of interest in exercise physiology are vast and often depend on the population of interest, but changes in energy expenditure, metabolism, and cardiovascular, respiratory, and neural systems have been heavily studied. Little is known about potential physiological changes that occur acutely after concussion and if and when these adaptations return to pre-injury levels due to the clinical recommendations for cognitive and physical rest.[21,64] The literature surrounding exercise physiology and concussion is sparse and is often limited to asymptomatic individuals or those with PCS.

Acute Exercise Sessions and Concussion. The metabolic cascade of concussion, discussed earlier in this review, is the only consistent physiological dysfunction at rest following concussion. However, a number of physiological differences between concussed and non-concussed subjects become apparent under conditions of physiological stress (ie. exercise). Asymptomatic concussed individuals have higher heart rates at lower intensities,[90] greater

change in heart rate throughout physical activity,[90] and higher blood pressure[176] than non-concussed controls despite no differences in heart rate variables between concussed and non-concussed participants at rest.[93,94,98] The authors state that the increases in heart rate during exercise following concussion are too large to be explained by detraining alone and instead suggest they reflect a cardiovascular abnormality following head trauma, which is a known phenomenon seen in more severe forms of brain injury.[90]

Adaptations following Aerobic Exercise Training. The large number of investigations into exercise physiology and the plethora of outcomes studied exceed the relevance of this project. Only the outcomes that will be evaluated in this study are discussed. Maximal oxygen consumption (VO_{2max}), which reflects the maximal rate of aerobic energy expenditure, adapts in response to aerobic exercise training.[19] The magnitude of improvements in VO_{2max} is influenced by a number of factors, including the intensity, duration, and frequency of exercise, the fitness level of the participant, and diet.[46] A consensus has not been established surrounding the optimal duration of exercise training programs, as studies have shown improvements after a few weeks or several months.[47,177] Exercise training programs are traditionally implemented for 6-8 weeks to ensure adequate time for physiological adaptation; however, one study found that the majority of improvements in VO_{2max} occur early (within 3 weeks) in the training period.[47] While this information is promising, the quick improvements may reflect neurophysiological adaptations, familiarization with exercise equipment, or poor study design and not true cardiovascular improvement, so results should be interpreted cautiously. Training at an intensity of 80-100% of VO_{2max} has been suggested to cause the largest improvements in aerobic capacity.[46,178]

Cardiopulmonary variables have also been shown to change following exercise training. Respiratory exchange rate (RER), equal to carbon dioxide production divided by oxygen consumption, is an indirect measurement of the contribution of lipids and carbohydrate fuel usage.[179-181] As exercise intensity increases, so does the RER, indicating a higher proportion of

fuel is coming from carbohydrate (as opposed to lipid) sources.[179] RER at the termination of maximal exercise is significantly correlated with changes in aerobic capacity.[182] Trained individuals have lower RER values compared to untrained individuals[183,184] and endurance training has been shown to decrease RER values.[185] Even a single bout of exercise has shown to reduce RER for up to 24-hours.[186]

Physiology Summary. Cardiopulmonary variables change in response to aerobic exercise training in healthy individuals. However, most aerobic training schedules are six or more weeks in length. As the aerobic training used in this study is designed to mimic the traditionally short concussion recovery window (10-14 days), little information exists to postulate whether significant improvements will be seen in cardiopulmonary outcomes following a six session training period in healthy individuals. Additionally, the recommendations for cognitive and physical rest following concussion have prevented researchers from understanding how these variables may change in response to concussion. ACTIVE training has the potential to influence, and improve, these variables in both healthy and concussed population. In concussed populations, this may minimize the amount of and psychological stress surrounding detraining

Summary

Physical activity has been shown as an effective form of rehabilitation in chronic stages of concussion recovery, but recommendations for cognitive and physical rest have prevented this therapy from being investigated acutely after injury. However, recent findings have suggested only three days of complete rest followed by activity as tolerated is the best treatment for concussion. This shift in the literature has opened the door for the evaluation of sub-symptom threshold exercise in the acute stages of recovery. Both exercise and concussion are known to influence a number of clinical outcomes (symptoms, cognition, balance, and vision), but the effect of an exercise training intervention on these variables remains known. Exercise training influences physiological variables (EEG, VO_{2max}, and cardiopulmonary variables) in healthy individuals, but if or how these variables are affected acutely after concussion, and if

they can be improved through exercise, has yet to be studied. Therefore, the purpose of this study is to examine the effect of an exercise-training program on clinical and physiological outcomes in healthy participants and to explore the effectiveness of exercise as rehabilitation in improving clinical, physiological, and return to activity outcomes in acutely concussed individuals. A secondary purpose of this study is to determine the feasibility of a sub-symptom exercise program in clinical sports medicine settings in both healthy and concussed participants.

CHAPTER 3

RESULTS GUIDE

Aim 1. To test the hypothesis that healthy college-aged participants randomized to ACTIVE training will have significantly improved symptom, balance, and cognition, but not vision, outcomes compared to healthy college-aged participants randomized to the control group.

- All clinical results discussed in Manuscript 2, entitled “A randomized controlled trial evaluating the effect of a brief aerobic training intervention on clinical concussion outcomes in healthy college-aged participants: The ACTIVE concussion management study” (Page 68 of the dissertation document)

Aim 2. To test the hypothesis that healthy college-aged participants randomized to ACTIVE training will have significantly improved resting-state EEG and cardiopulmonary outcomes compared to healthy college-aged participants in the control group.

- Cardiopulmonary outcomes discussed in Manuscript 3, entitled “A brief aerobic training protocol in healthy subjects: The ACTIVE concussion management study” (Page 81 of the dissertation document)
- EEG outcomes discussed in Manuscript 4, entitled “A randomized controlled trial investigating the effect of aerobic exercise training on electroencephalography in healthy participants: The ACTIVE concussion management study” (Page 93 of the dissertation document)

Aim 3. To test the hypothesis that ACTIVE training is safe and feasible in college-aged participants.

- All safety and feasibility outcomes discussed in Manuscript 1, entitled “A randomized controlled trial investigating the feasibility and adherence to an aerobic training program in healthy individuals: The ACTIVE concussion management study ” (Page 55 of the dissertation document)

CHAPTER 4

MANUSCRIPT 1

A randomized controlled trial investigating the feasibility and adherence to an aerobic training program in healthy individuals: The ACTIVE concussion management study

Introduction

Concussions are the most frequently occurring traumatic brain injury resulting from sport[187] and represent a large public health concern. Concussions can result in recognizable signs and reported symptoms as well as cognitive and balance dysfunction.[115] Most individuals recover from concussion within two weeks of injury,[21] yet up to 500,000 people per year report persistent dysfunction for months to years.[10] This small but significant minority is forcing researchers and clinicians to reconsider passive treatment strategies and progress towards active rehabilitation paradigms capable of mitigating deleterious injury consequences.

Current clinical guidelines support cognitive and physical rest for concussed individuals until symptom resolution, followed by gradual return to activity.[21,64] However, the literature surrounding the effectiveness of prescribed rest is mixed, with many studies finding no benefit or harm.[12,105,110] Current evidence suggests rest should persist for three days followed by a re-integration of activity as tolerated by the patient.[12] These emerging recommendations have created a shift in management techniques, with more active treatment strategies being considered for clinical use.

Physical activity interventions may offer some clinical strategies designed to address the shortcomings of prescribed rest and mitigate persistent symptoms. Several studies support

exercise implementation in chronic concussion recovery stages, with exercised individuals achieving shortened symptom durations,[5,6,66,67] decreased depression scores,[68] and improved cognition and mood[68] compared to those treated conventionally with rest. Clinicians still continue to use caution when prescribing exercise treatments given the known acute physiological disruptions, although no serious adverse events are reported in previous studies.[63] Such caution is consistent with animal models suggesting exercise too close to injury may be detrimental to recovery.[188] To inform acute concussion exercise guidelines, interventions should first undergo a thorough evaluation of feasibility and adherence in healthy individuals, before implementation in concussed patients. To our knowledge, few studies have examined the feasibility and adherence of acute concussion rehabilitation programs related to exercise.[57] The purpose of this Phase I clinical trial is to establish the feasibility and adherence of an aerobic training program in healthy, recreationally active university students. Phase 1 trials examine a proposed treatment in small cohorts to evaluate, describe adherence, and identify potential unintended effects of treatment. The intent of this research is to ensure that healthy university students are adherent to a brief aerobic training program and to provide a foundation for future applications of active interventions in concussion management for injured subjects.

Methods

Design: A parallel-group, unblinded randomized controlled trial assessed the effect of acute concussion therapy intervention (ACTIVE) training on feasibility and adherence outcomes in healthy participants. All subjects completed a pre- and post-intervention maximal exercise test approximately 14 days apart. Participants randomized to ACTIVE training completed six, 30-minute training sessions between maximal exercise tests, while non-training participants received no intervention.

Subjects: Recreationally active individuals (n=40) between the ages of 18-30 years were recruited for this study. Recreationally active was defined as 30+ minutes of physical activity ≥3 days per week. Participants were excluded if they sustained a head injury within the year prior

to enrollment, had any lower extremity injury preventing stationary cycling or balancing on one leg, used recreational drugs, or had known cardiovascular health issues. Participants had no contraindications to exercise based upon the Physical Activity Readiness Questionnaire, a general medical history, and an electrocardiogram as determined by the study physician who reviewed all medical documents and provided medical clearance. All participants meeting inclusion criteria provided informed consent approved by the Institutional Review Board at the University of North Carolina at Chapel Hill (IRB #15-2387).

Procedures: Participants were randomized into ACTIVE training (intervention) or non-training (no intervention) groups using a computer-generated randomization sequence with block sizes of four. Participants completed an orientation session and two test sessions in a controlled, laboratory setting. The orientation session familiarized participants with testing equipment and provided instruction on pre-testing guidelines (hydrate prior to scheduled session and avoid eating within two hours, exercise within 12 hours, alcohol within 48 hours, and diuretic medication within 7 days). For the maximal cardiopulmonary exercise test (CPET) familiarization session, participants were fitted for a respiratory mask and seat height was adjusted for proper pedaling mechanics on the cycle ergometer. Participants underwent the earliest stages of the CPET following a warm up at no resistance to minimize a learning effect associated with subsequent CPET administrations. Test sessions were conducted roughly 14 days apart to best approximate typical duration between incident concussion and clinical recovery.[42] All exercise sessions were completed on a Lode stationary electric-brake bike (Lode, Gronigen, The Netherlands) to make this intervention more translatable to acutely concussed participants, as treadmill protocols may be difficult for participants with balance deficits.[189]

Maximal Exercise Test: All participants completed a CPET at both test sessions, following standardized procedures set forth by the American College of Sports Medicine (ACSM).[17] A physician and a certified athletic trainer team were on call at a nearby location and

prepared to respond in the case of an adverse event. Before each CPET, the metabolic cart was calibrated following manufacture guidelines. Participants began the maximal exercise test at 50W and increased by 50W for the first two stages and 30W every stage following. Each stage lasted for two minutes for the first 10 minutes, with one-minute stages following volitional exhaustion. Ventilatory outcomes were collected using a ParvoMedics TrueOne® 2400 metabolic cart (ParvoMedics, Sandy, UT). Heart rate was collected every minute and Borg rating of perceived exertion (RPE) was collected in the last 30 seconds of every testing stage. Blood lactate was collected using a Lactate Plus analyzer (Sports Resource Group, Hawthorne, NY) three minutes following test completion. For a CPET to be valid, at least three of the following criteria were met: a) plateau in maximal volume of oxygen values (≤ 2.1 ml/kg/min) with increase in exercise intensity, b) respiratory exchange ratio (RER) ≥ 1.10, c) RPE ≥ 17, d) lactate ≥ 8.0mmol/L, and e) heart rate (HR) within 10 beats of age predicted heart rate max (220-age). All CPETS meet this requirement except two.

ACTIVE Training: Participants in the ACTIVE training group completed six 30-minute training bouts on the stationary bike between test sessions. Each session included a 3-minute warm up and 3-minute cool down. The first training session was conducted at a workload equal to 60% of maximal oxygen consumption (VO_{2max}) achieved on the baseline CPET and subsequent sessions were progressively more difficult, with the final session conducted at 80% of VO_{2max}. This progression from 60-80% of VO_{2max} aligns with the exercise prescription guidelines set forth by the ACSM.[190] To ensure participants were training at the appropriate intensity, oxygen consumption levels were checked at the 5-, 15-, and 25-minute mark (3-minute recordings) during training sessions, with adjustments occurring as needed to ensure target exercise intensity was achieved. The lead author, who has over seven years' experience in this population, supervised all training sessions, assisted by an exercise physiologist with over 20 years' experience working in exercise prescription in clinical populations.

Outcome Measures: Feasibility, adherence, and adverse event outcomes were recorded during all study sessions. These metrics included evaluations of the: a) study protocol and randomization procedures effectiveness, b) exercise safety and adherence, c) progressive intensity of the ACTIVE training procedures, and d) potential energy imbalance across randomization arms (evaluated using Fitbit (Fitbit®, Boston, Massachusetts) Charge HR devices). This study defines an adverse event as any unanticipated, unfavorable medical occurrence associated with a subject's participation in research.

Statistical Analysis: Intention-to-treat analyses were performed; groups were analyzed based on the randomization assigned upon enrollment regardless of participant adherence. Descriptive analyses were completed for all outcome variables. Chi-square and independent samples t-tests were used to assess randomization effectiveness. Mixed-design linear regressions using restricted maximum likelihood estimators were conducted to determine if energy expenditure differed between groups. A priori alpha was set to 0.05. All statistical analyses were completed in SAS (Version 9.4; SAS Institute, Inc., Cary, North Carolina). Sample size was determined using a priori power analyses conducted in G*Power (Version 3.1, Düsseldorf, Germany). Thirty-six participants (18 per group) were needed and 40 participants were recruited to account for potential attrition.

Results

Study Protocol and Randomization Procedures Effectiveness. Forty-five participants were screened during a seven-month period from August 2016 to February 2017, with data collection continuing through March 2017. Forty-one individuals (91%) met the inclusion criteria, with forty participants (98%) enrolled and retained (**Figure 4.1**). Participants were randomized into ACTIVE training or non-training groups upon study enrollment. No significant group differences were observed for age, sex, height, weight, concussion history, premorbid conditions, or self-perceived fitness levels (**Table 4.1**).

ACTIVE Training Safety and Adherence. A total of 77 CPETs and 110 ACTIVE training sessions were completed with no adverse events reported in conjunction with the exercise protocols. One participant (2.5%) fainted during venipuncture, a known risk of phlebotomy that the research team was adequately prepared for. Three (3.6%) CPETs were missed, due to the participant fainting during the preceding venipuncture (n=1) and calibration issues associated with software malfunctions of the metabolic cart computer (n=2). Ten out of 120 training sessions (8.3%) were missed with reasons including: unforeseen university closure due to inclement weather (n=3), illness (n=4), and forgot about scheduled session (n=3). No exercise sessions were ended early.

Progressive Intensity Across ACTIVE Training Sessions. Within the intervention arm, heart rate significantly increased ($F_{(5,101)}$=4.57, p<0.001) and rate of perceived exertion tended to increase ($F_{(5,95)}$=2.11, p=0.07) with subsequent training sessions. Change in symptom scores from pre to post exercise and workload at training termination did not significantly differ across sessions (**Table 4.2**). Target training intensity progressed from: 56-60% of $VO2_{max}$ (session 1), 60-64% of $VO2_{max}$ (session 2), 64-68% of $VO2_{max}$ (session 3), 68-72% of $VO2_{max}$ (session 4), 72-76% of $VO2_{max}$ (session 5), 76-80% of $VO2_{max}$ (session 6). Participants were tolerant of the prescribed training intensity, with thirteen participants (65%) able to exercise within the target intensity range at all six training sessions and four participants (20%) during five sessions. Three participants (15%) were unable to tolerate the exercise intensity at the final three training sessions (training above 70% of $VO2_{max}$ for 30 minutes) and the exercise prescription was modified for these participants.

Energy Imbalance Across Randomization Arms. Fitbit outcomes were reported in daily values and split into three groups: intervention participants on days with a scheduled ACTIVE training session (ACTIVE Training), intervention participants on days without a scheduled ACTIVE training session (ACTIVE No Training), and non-training group participants (Non-Training). More minutes of total activity (ACTIVE Training: 284.8 ± 123.7; ACTIVE No Training:

264.0 ± 108.9; Non-Training: 252.3 ± 118.3; p=0.47), and number of steps taken (ACTIVE Training: 12080 ± 4959; ACTIVE No Training: 10555 ± 4780; Non-Training: 10051 ± 4897; p=0.24) were higher on days of scheduled ACTIVE training sessions, although these results did not reach statistical significance. Minutes of low, moderate, and high intensity activity were not different between groups (p>0.05).

Discussion

Active rehabilitation strategies have potential as a therapeutic intervention in concussion management. However, few programs have been implemented acutely, due in part to feasibility concerns. There is a need for detailed and thorough evaluations of aerobic exercise programs in healthy and concussed individuals. These results indicate that ACTIVE training is a feasible aerobic training program in active young adults. Participants were adherent and tolerant to the training protocol and outcomes presented here, particularly symptom and perceived exertion changes throughout ACTIVE training, can serve as normative data for future research in concussed populations.

Healthy university students were adherent to the ACTIVE training schedule and no adverse events occurred throughout this study, besides one expected issue commonly associated with phlebotomy. Most participants (60%) completed all six training sessions over the two-week intervention interval, with every participant completing the a priori level of acceptable adherence of four sessions. In total, only 6.5% of exercise sessions were missed throughout this study, with missed sessions distributed throughout the training period. Previous concussion intervention protocols show similar levels of adherence for both healthy[191] and concussed[58,66] populations. Additionally, the high recruitment and low dropout rates in this study meet levels reported in other studies.[58] This information suggests the adherence to ACTIVE training reported here may be similar in concussed populations; however, most concussion rehabilitation interventions fail to report information surrounding protocol feasibility or

adherence[14,68,80,81] and limits our ability to discuss the translation of ACTIVE training to concussed populations with more certainty.

Participants were tolerant of ACTIVE training intensity. The significant increases in heart rate throughout the training period, combined with trend towards higher perceived exertion and training resistance, support that the progressively increasing intensity of the training program was appropriately met. Changes in symptoms score pre to post exercise and missed sessions did not significantly differ throughout the training period, suggesting participants did not experience overtraining or burnout. This study was comprised of young, healthy adults who volunteered for participation and clinical populations, such as acutely concussed individuals, may display depressed tolerance to training intensity, requiring further evaluation. Other studies report a small portion of concussed individuals cannot tolerate aerobic exercise at moderate intensities due to symptom exacerbation, but lowering the exercise workload can eliminate this negative response without further issue.[58,67]

Fitbit outcomes failed to reach statistical significance. Minutes of total activity and step counts trended towards higher levels for intervention participants on scheduled training days, with approximately 20 (compared to days no scheduled training sessions) and 32 (compared to non-training group) more minutes of physical activity was completed. This additional activity on scheduled ACTIVE days suggests that training was completed in addition to, not in place of, normal physical activity for intervention participants. Minutes of moderate and vigorous activity were not significantly different between groups; however, all ACTIVE training sessions were completed on a stationary cycle ergometer and Fitbit monitors are known to significantly underestimate energy expenditure during cycling activities.[192,193] The exercise intensity recorded during training sessions may have been incorrectly classified, which may explain why more total minutes of activity, but not moderate or vigorous minutes, was higher on days of scheduled training sessions. The Fitbit was prone to missing data, even on days when research team

members verified the device was appropriately worn and charged, highlighting potential limitations of using Fitbit devices as research tools.

This study has implications for physical activity interventions as a concussion management intervention. Concussion is known to disrupt cerebral metabolism,[89] cerebrovascular regulation,[61] and autonomic nervous system[65] functioning and these physiological deficits may represent the physiological underpinning of clinical concussion symptoms and deficits. Aerobic exercise influences these physiological domains and may be a mechanistic approach to facilitating recovery, providing additional benefits to concussed persons above those shown in healthy cohorts.

Our study using healthy participants showed that moderate training intensities could cause up to a 6-point increase in symptoms. Therefore, a small symptom increase following exercise in concussed patients may not be of medical concern. Reliable change scores and clinical judgment from a supervising medical professional may represent better methods of determining a clinically meaningful symptom increases. Other studies in concussed cohorts found that high symptom increases following exercise can be easily managed by reducing exercise intensity[67] and no serious adverse events have been reported following exercise in concussed patients.[57,58,66,67] ACTIVE training used a training schedule of three sessions per week, which was feasible in this cohort. Rehabilitation schedules in other settings are often completed between 3-5 days per week and previous studies evaluating home based exercise-training programs in chronically concussed cohorts target six days of exercise per week,[66] supporting the idea that ACTIVE training could be feasible in injured populations. This study provides support that aerobic exercise programs are feasible in healthy populations and this serves a starting point for evaluating similar exercise interventions in acutely concussed populations.

Limitations

ACTIVE training is a feasible intervention in healthy young adults, but concussed participants may have a differential response to exercise due to ongoing clinical and physiological deficits. Concussed participants should be closely monitored and exercise paradigms should be kept below individual symptom threshold. There is no guarantee that these results are translatable to other populations, such as children, elite athletes, or acutely concussed individuals.

Conclusion

Aerobic exercise has a number of potential benefits specific to concussed patients. Thorough evaluations of feasibility are necessary to ensure the potential benefits outweigh any risk of harm. ACTIVE training is feasible program for healthy, recreationally active university students, who were able to adhere to the designed exercise protocols. This study has potential implications for trials of concussion management protocols aimed at stimulating exercise training as a clinical intervention. The results of this study suggest that acute aerobic exercise feasible intervention and serves as a starting point for future acute concussion exercise rehabilitation interventions.

Practical Implications

- ACTIVE training is a feasible aerobic exercise program for healthy university students and no adverse events were reported.
- ACTIVE training had high adherence in healthy university students, with the majority of participants completing all six training sessions within a 14-day period.
- Healthy participants were able to tolerate the progressively intense workloads associated with ACTIVE training, but acutely concussed populations may have depressed tolerance due to ongoing clinical and physiological deficits.

Tables

Table 4.1. Effectiveness of randomization procedures as measured by differences in demographic information between groups.

	Non-Training Group (n=20)	**ACTIVE Training Group (n=20)**	***P* Value**
Age	21.15 ± 2.70	20.4± 1.14	0.25
Sex	10 male, 10 female	10 male, 10 female	1.00
Height (cm)	174.3 ± 9.30	173.5 ± 11.44	0.81
Weight (kg)	71.1 ± 11.16	71.2 ± 12.82	0.98
Days Between Sessions	12.68 ± 3.04	14.77 ± 2.80	0.07
No. Previous Concussions	0.55	0.27	0.35
Premorbid Conditions			
ADHD	2	2	1.00
ADD	1	1	1.00
Learning Disability	0	1	0.31
Seizure	0	0	1.00
Depression	0	3	0.71
Psychiatric	0	0	1.00
Anxiety	0	2	0.14
Migraines	2	0	0.14
Any Condition	4	6	0.46
Family Condition	7	9	0.52
Self-Perceived Fitness*	4.1± 0.55	3.75 ± 0.63	0.07

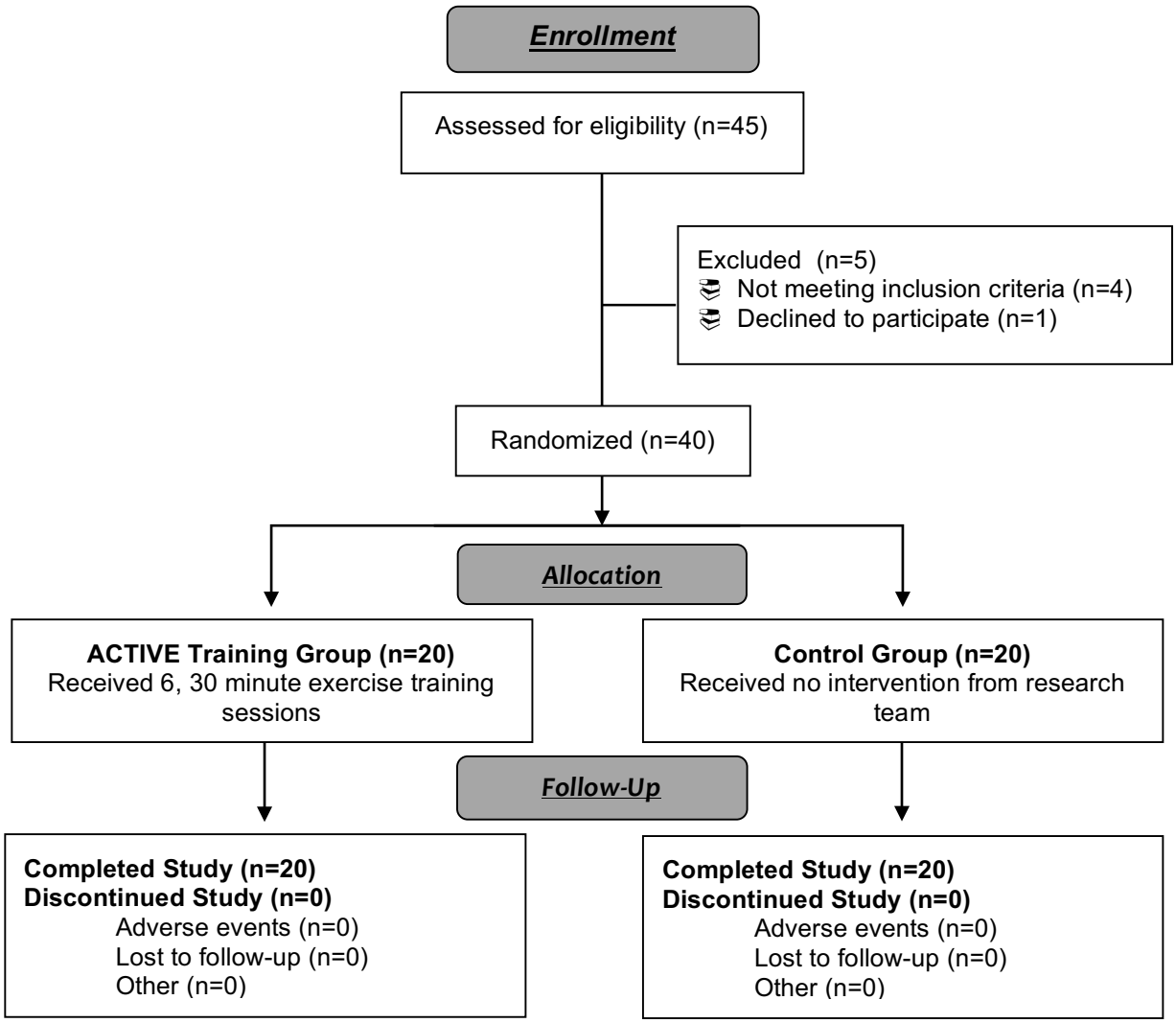
*Self-perceived fitness was rated on a 1-5 scale, where 1=much less fit than your peers, 3=just as fit as your peers, and 5=much more fit than your peers.

Table 4.2. Adherence and tolerance of all ACTIVE training session, with results from the first maximal exercise test for reference.

	1st Maximal Exercise Test	**ACTIVE Training 1** *(56-60% of Max)*	**ACTIVE Training 2** *(60-64% of Max)*	**ACTIVE Training 3** *(64-68% of Max)*	**ACTIVE Training 4** *(68-72% of Max)*	**ACTIVE Training 5** *(72-76% of Max)*	**ACTIVE Training 6** *(76-80% of Max)*
∆ Total Symptom Score	2.2 ± 5.0	0.5 ± 2.2	0.4 ± 1.9	0.4 ± 1.9	0.1 ± 2.0	0.6 ± 1.5	0.4 ± 1.9
HR at Termination	180.9 ± 9.7	143.3 ± 12.6	141.1 ± 12.1	146.5 ± 14.7	152.1 ± 11.9	155.9 ± 11.2	158.2 ± 12.1
RPE at Termination	18.2 ± 1.4	12.9 ± 2.1	12.6 ± 1.7	13.2 ± 1.35	13.6 ± 1.6	13.8 ± 1.6	14.2 ± 1.6
Workload (W) at Termination	239.7 ± 60.8	105.7 ± 41.2	107.1 ± 35.3	117.1 ± 37.7	116.6 ± 34.9	125.9 ± 34.3	129.8 ± 34.6
Missed Sessions	0 (0%)	2 (10%)	3 (15%)	2 (10%)	0 (0%)	1 (5%)	2 (10%)
Adverse Events	0	0	0	0	0	0	0

Figure Legends

Figure 4.1. Profile of the randomized controlled trial.



CHAPTER 5

MANUSCRIPT 2

A randomized controlled trial evaluating the effect of a brief aerobic training intervention on clinical concussion outcomes in healthy college-aged participants: The ACTIVE concussion management study

Introduction

Concussions are the most common form of traumatic brain injury[194] and account for approximately 5% of all injuries reported in National Collegiate Athletic Association athletes.[195] Current concussion diagnosis and management is centered around a clinical evaluation along with symptom, balance, and cognitive testing.[64] Best practice guidelines advocate for physical and cognitive rest until symptom resolution, with most individuals recovering within 7-10 days.[21] A small but significant minority of individuals fail to fully recover with rest alone and show persistent concussive deficits for weeks or months following injury.[10] Experts recommendations are shifting towards more active recovery strategies in hopes of improving outcomes and mitigating persistent concussive dysfunction.[12]

Aerobic exercise is a novel concussion rehabilitation method. Several studies have explored the potential benefits of physical activity on concussion recovery with consistent findings of reduced symptom burden and improved cognition and mood outcomes in chronic individuals, with no serious adverse events reported.[6,57,66-68] The literature addressing the effect of exercise on concussion recovery is small yet exceedingly positive. However, these studies are often limited by long time intervals between injury and exercise onset, little internal control,

and a small scope of primary outcomes, with most studies focused exclusively on concussion recovery time and symptom burden.

Exercise positively affects multiple outcomes in non-injured populations. Acute exercise bouts improve symptoms[26] and decreased balance[22,196] in healthy populations, while chronic aerobic training is known to positively affect cognition and memory, especially in aging adults.[111] However, no studies have directly evaluated the effect of a brief aerobic training on clinical concussion assessments. Understanding how an aerobic exercise based concussion rehabilitation program may affect clinical outcomes in healthy populations is imperative, as clinicians must ensure improvements seen post-injury are a result of recovery and not a byproduct of elevated physical activity to ensure the highest standards for athlete safety.

Therefore, the primary purpose of this study was to determine the effect of an aerobic exercise program designed for use in acute concussion rehabilitation (acute concussion therapy intervention-ACTIVE training) on clinical concussion metrics in a healthy, collegiate population. We hypothesized that symptom, cognitive, and balance outcomes would improve with the exercise intervention, but visual outcomes would not change.

Methods

Participants

Individuals between the ages of 18-30, who participate in at least 30 minutes of physical activity three or more days per week were recruited for this study. Participants were excluded if they sustained a head injury within the past year, had any lower extremity injury preventing them from stationary bike cycling or balancing on one leg, used recreational drugs, or had any cardiovascular abnormalities. The study physician provided medical clearance for all participants based upon a thorough medical history and electrocardiogram. All enrolled participants provided informed consent approved by the Institutional Review Board at the University of North Carolina at Chapel Hill (IRB #15-2387).

Intervention

The methods used in this study are described in detail in Teel XXX. Briefly, a parallel-group, unblinded randomized controlled trial was designed to assess the effect of ACTIVE training on clinical outcomes. Participants were randomized into ACTIVE training (intervention) or non-training (no intervention) groups upon study enrollment using a computerized-generated randomization sequence with block sizes of four.

All participants completed clinical concussion metrics and a maximal exercise cycling protocol at two test sessions approximately 14 days apart. Non-training group participants received no intervention between test sessions while participants in the ACTIVE training group completed six, progressively intense 30-minute training bouts (60-80% of VO_{2max}). All exercise sessions were completed in a controlled laboratory setting using a Lode Corival cycle ergometer (Lode, Gronigen, The Netherlands) and oxygen consumption was checked periodically to ensure target training intensity was met.

The lead author with over seven years experience using the clinical concussion metrics in this study supervised all sessions for all participants. An experienced exercise physiologist supervised the maximal exercise testing and ACTIVE training protocols. No changes to methods or subject recruitment were made throughout the trial. As this study focused on healthy, recreationally active participants, no guidelines to prematurely stop the trial were implemented.

Main Outcome Measures

The primary outcome measures for this study were changes in clinical concussion metrics. As concussed individuals are known to display deficits in cognition, balance, symptomology, and vision, widely used clinical metrics to evaluate these domains were chosen. All primary outcomes measures were assessed at both test sessions, and included the following: a) CNS Vital Signs, b) Balance Error Scoring System, c) Standardized Assessment of Concussion, d) Graded Symptom Checklist, and e) Vestibular/Ocular Motor Screening.

CNS Vital Signs

CNS Vitals Signs (CNS) is a 30-minute computerized neurocognitive assessment that evaluates attention span, working memory, response variability, problem solving, and reaction time. CNS Vital Signs uses stimuli randomization when possible to reduce practice effects; on-screen instructions and short practice tests are provided. CNS produces standardized scores that scales outcomes into categories (<70= very low, 70-79= low, 80-89= low average, 90-110= normal, >100= above average) based on an age-matched normative dataset. Standardized scores for Neurocognitive Index, Composite Memory, Verbal Memory, Visual Memory, Psychomotor Speed, Reaction Time, Complex, Attention, Cognitive Flexibility, Processing Speed, Executive Function, Reasoning, Simple Attention, and Motor Speed were used in this study.

Standardized Assessment of Concussion (SAC)

The SAC is a five-minute sideline evaluation that tests orientation, immediate and delayed memory, and concentration. Orientation is evaluated through asking the participation the month, date, day of the week, year and time. Immediate memory has the participant repeat a list of five words that has been read out loud, three times. Concentration is tested first by repeating a number string followed by stating the months of the year, both in reverse order. Delayed memory asks participants to recall as many of the five words from the immediate memory word list as possible. Total SAC score (out of 30) is the primary outcome of interest from this assessment.

Balance Error Scoring System (BESS)

The BESS uses double leg, non-dominant single leg, and tandem stances (non-dominant leg in back) over two support conditions (firm and foam) to assess static balance. Each 20-sec trial is done with eyes closed and hands on hips. A test evaluator scores participants on errors committed during each trial (maximum errors per trial = 10). Errors include

removing hands from hips, opening eyes, step or fall, hip abduction/flexion >30°, lifting the forefoot/heel off the testing surface, and remaining out of the test position for more than five seconds. Total BESS score (out of 60) over all six conditions was used in this study, with lower scores representing better balance.

Graded Symptom Checklist (GSC)

The GSC lists 27 common concussive symptoms for participants to rank on a Likert scale (0= not present, 1= mild to 6= severe). The total symptom score, which encompasses both presence and severity of symptoms, was used in this study and lower scores represent better outcomes.

Vestibular/Ocular Motor Screening (VOMS)

The Vestibular/Ocular Motor Screening (VOMS) is a five-minute visual assessment that can be completed on the sideline or in clinical settings. The VOMS evaluates saccade, pursuit, convergence, vestibular-ocular reflex, and visual motion sensitivity domains. Participants are asked to self-report four symptoms (headache, nausea, dizziness, and fogginess) prior to and immediately following assessment in each visual domain. Near-point convergence distance (in cm) is the outcome of interest in this study.

Statistical Analysis

All statistical analyses were completed in SAS (Version 9.4; SAS Institute, Inc., Cary, North Carolina). Descriptive analyses were completed for demographic and primary outcomes. Intention-to-treat analyses were performed, meaning that groups were analyzed based on the randomization received upon enrollment regardless of adherence. Separate 2 (group) by 2 (session) ANOVAs were completed for all primary outcomes. Demographics and primary outcomes did not differ between groups at the first test session; therefore, no covariates were added to any statistical model. Means were calculated using a 10% Winsorized method to control for potential outliers without reducing sample size.[197] For all outcomes, 80% reliable

change indices (RCIs) were calculated to determine if any potential mean differences had clinical relevance. A priori alpha was set to 0.05. A power analyses (G*Power Version 3.1, Düsseldorf, Germany) determined the number of participants needed to adequately power all primary outcomes of interest was 36 (18 per group). Forty participants were recruited to account for potential attrition or missing data.

Results

Participants were recruited and tested from August 2016 to March 2017. Forty-five individuals were screened for participation; four individuals did not meet inclusion criteria due to health concerns that precluded them from receiving medical clearance from the study physician. One participant who met the inclusion criteria declined participation. The remaining forty participants were enrolled into the study, with no participants lost to follow up. A more detailed report regarding the safety and feasibility of the ACTIVE training intervention has previously been published (Teel et al. XXXX).

Twenty participants were randomized to the ACTIVE training group. No significant differences in baseline characteristics were observed between groups (**Table 5.1**). Most participants (n=12) completed all six training sessions, with all participants completing at least four sessions. Reasons for missed sessions include illness (n=4), unforeseen university closure (n=3), and schedule conflicts (n=3). No adverse events were reported during the study.

Primary outcomes by group and session are shown in **Tables 5.2 & 5.3**. Main effects of session were found for composite memory (t_{37}=2.34, *P*=0.025), verbal memory (t_{37}=2.09, *P*=0.044), cognitive flexibility (t_{37}=2.92, *P*=0.006), executive function (t_{37}=2.82, *P*=0.008), reasoning (t_{34}=2.42, *P*=0.021), total symptom score (t_{36}=2.36, *P*=0.024), and near-point convergence (t_{36}=2.05, *P*=0.047). Both composite and verbal memory significantly worsened at the second test session, with all other domains significantly improving between sessions. The intervention group performed significantly better on complex attention (t_{38}=2.13, *P*=0.040) and simple attention (t_{38}=2.07, *P*=0.045) domains than the non-training group. These group

differences were not present at baseline alone (P>0.05). A significant interaction effect was found for total symptom score ($F_{1,36}$=4.41, P=0.042), with the intervention group significantly improving between the first and second test session. Mean differences did not exceed the 80% RCI calculated from this study for any outcome of interest.

The SAC overall score, GSC total symptom score, and VOMS near-point convergence distance (cm) are known to be limited by ceiling (SAC) or floor (GSC and VOMS) effects. Chi-squared analyses were run to determine if the proportion of individuals at the ceiling or floor differed over time. No differences (SAC: χ^2=2.99, P=0.08; GSC: χ^2=1.88, P=0.17; VOMS: χ^2=0.12, P=0.72) were found between sessions.

Conclusions

The ACTIVE training produced significant main effects and interactions; however, these values were within reliable change and indicate the high stability of clinical concussion outcomes in response to aerobic training. Exercise following concussion has been shown to improve outcomes in chronic recovery stages[6,68] and clinicians are beginning to evaluate their effectiveness more acutely. Little data exists to suggest if and how aerobic exercise training can influence clinical diagnostic and management tools, which can have profound affect on return-to-play and athlete safety outcomes. ACTIVE training was evaluated in healthy, recreationally active young adults to establish expected exercise response changes to create the foundation for future research in concussed cohorts.

Previous literature investigating exercise and clinical concussion assessments has focused on the immediate effects of a single exercise bout.[22,25-27] Immediate and delayed verbal memory scores measured via computerized neurocognitive evaluations are significantly impaired following a maximal exercise test,[23] but cognitive domains measured via sideline assessments[145,198] are not influenced by acute exercise. Most studies show BESS scores worsen following physical activity and take up to 20 minutes to recover.[22,28,135] Symptom scores increase following intense exercise;[25] however, some symptom clusters improve following

moderate intensity exercise.[26] The effects of exercise on vision are unknown. No previous studies have investigated a period of aerobic exercise training on clinical concussion outcomes in healthy populations, making comparisons to ACTIVE training difficult.

A significant overall interaction effect was found for the Graded Symptom Checklist, driven by improvements in the intervention group between sessions. The intervention group reported a mean symptom score of 5.10 at the first time point. Previous studies show that mean total symptom scores fluctuate around 1-3 points,[23,25,90] suggesting that intervention group, for unknown reasons, reported high symptoms scores at the first test session and regressed to the mean at the second test session. Near point convergence distance significantly increased at the second test session for both training and non-training groups; however, group means for all sessions are within previously established normative values (<5cm) for near-point convergence distance.[199] Significant main effects of group and time were reported on a number of computerized cognitive assessments. However, all mean differences in cognitive outcomes were within reliable change scores established in this study and those previously established in the literature,[33,200] suggesting the findings were due to learning effects or inherent variability in the test and participants themselves. Together, the results of this study indicate that clinical concussion outcomes have high stability in response to a brief aerobic training protocol, which represents an important clinical finding.

Aerobic exercise is becoming a popular concussion treatment option as previous studies suggest exercise positively influences symptom,[66,68,201] balance,[67] and cognitive[68] domains in prolonged recovery populations. In contrast to the concussed literature, this study suggests that aerobic exercise itself, at least in a short duration training window, does not influence clinical concussion outcomes in healthy participants. Recurrent concussion risk is highest within the first 10 days of initial injury.[122] Ensuring rehabilitation interventions do not arbitrarily improve clinical concussion outcomes are critical for ensuring athlete safety, particularly as rehabilitation paradigms are initiated in more acute recovery phases. The stability of clinical assessments in

response to ACTIVE training is a critical finding; this allows clinicians prescribing exercise therapy to interpret outcomes as currently advised, eliminating the need for adjusted scores, and providing confidence that improvements in these outcomes in injured patients are the result of healing and are not a byproduct of exercise alone.

The potential benefits of ACTIVE training far outweigh potential risks in young, healthy individuals. Aerobic exercise is a relatively cheap and easy form of rehabilitation, with cardiovascular[202-204] and mental[205] benefits. Additionally, the risk of major adverse events associated with physical activity are low (<5%) for healthy young populations.[56] Aerobic exercise may hold additional benefits for concussed individuals as it can target the underlying physiological deficits following injury[61,65,89] and expedite recovery; however, concussed individuals with visual, vestibular, and cervicogenic dysfunction may benefit from additional therapies in supplement to exercise training.

This study provides further theoretical support for the use of exercise interventions as concussion rehabilitation. Previous studies suggest concussion symptoms[42] and neurometabolic deficits[89] have peaked and begin returning to baseline levels within the first few days of injury. Prescribed rest is recommended only for the first three days, following by activity as tolerated by the participant.[12] Our data suggest that moderate levels of exercise have little effect on symptoms in healthy populations (mean increase of less than 1 point following exercise). Combined with the previous concussion literature, the high safety, adherence, and tolerability of ACTIVE training in healthy participants, described in more detail elsewhere (Teel XXX), supports the notion that ACTIVE training may be used in acute concussion recovery stages. However, future studies should evaluate the adherence and tolerability of ACTIVE training in concussed populations and all exercise training sessions for acutely concussed persons should be kept below symptom exacerbation thresholds and closely supervised by a medical professional.

Limitations

While assessing outcomes in healthy populations is considered the first phase of clinical trials, results shown in healthy individuals may not directly translate to concussed participants who may have a differential response to exercise training. As both concussion and aerobic exercise can affect psychological outcomes, future studies should evaluate the influence of concussion rehabilitation on mental health outcomes such as anxiety and depression. Efforts were made in the study design and analysis to make results as generalizable as possible, but future studies should evaluate the effects of aerobic training in other populations, including youth and elite level athletes, as findings may not directly transfer.

What are the new findings?

- Clinical concussion outcomes remain stable in response to the ACTIVE training protocol, as mean differences are retained within 80% RCIs.
- The effect of aerobic training in this healthy cohort is in contrast with the concussion literature, which shows meaningful improvements in symptom and cognitive outcomes.
- Clinical concussion management tools can be interpreted as directed without the need for adjusted scores for individuals undergoing exercise therapy.

Tables

Table 5.1. Demographic characteristics for all participants. No significant group differences were observed.

Variable	Non-training Group (n=20)	ACTIVE Training Group (n=20)	P-Value
Age (yrs)	21.2 ± 2.7	20.4 ± 1.1	0.25
Sex	10 male, 10 female	10 male, 10 female	1.00
Height (cm)	174.3 ± 9.3	173.5 ± 11.4	0.81
Weight (kg)	71.1 ± 11.1	71.2 ± 12.8	0.98
Grade Point Average*	3.4 ± 0.4	3.3 ± 0.3	0.38
Premorbid Conditions†			
Self	4	6	0.47
Immediate Family	7	9	0.52
Concussion History (N)			
Yes	5	4	0.71
No	15	16	

*Grade point average is a metric of academic achievement used in the United States. Grade point average is on a 0-4 scale, with 4 representing the best academic achievement.
†Premorbid conditions include ADD, ADHD, learning disability, seizure disorder, depression, anxiety, psychiatric condition, and migraines. Immediate family includes parents and siblings.

Table 5.2. Means, standard deviations, and 95% confidences interval for all CNS Vital Signs outcomes at each session for ACTIVE training and non-training groups.

	Outcome	Non-training Group (n=20)		ACTIVE Training Group (n=20)		Adjusted *P* Value			80% RCI
		Session 1	Session 2	Session 1	Session 2	*Session*	*Group*	*Group X Session*	
CNS Vital Signs	Neurocognitive Index	97.60 ± 9.49 (93.16, 102.43)	98.55 ± 9.75 (93.99, 103.11)	101.20 ± 8.27 (97.33, 105.07)	103.63 ± 7.60 (99.97, 107.29)	0.14	0.13	0.61	7.69
	Composite Memory	105.45± 15.21 (98.34, 112.57)	98.15 ± 16.19 (90.57, 105.73)	109.30 ± 11.22 (104.05, 114.55)	107.21 ± 13.51 (100.70, 113.72)	0.02	0.12	0.22	15.73
	Verbal Memory	102.60 ± 15.26 (95.46, 109.74)	97.90 ± 16.17 (90.33, 105.47)	109.05 ± 12.36 (103.26, 114.84)	103.74 ± 16.06 (96.00, 111.48)	0.04	0.15	0.84	18.77
	Visual Memory	106.20 ± 13.24 (100.00, 112.40)	98.50 ± 16.43 (90.81, 106.19)	106.45 ± 9.54 (101.99, 110.91)	107.37 ± 11.94 (101.62, 113.21)	0.14	0.19	0.06	18.01
	Psychomotor Speed	105.15 ± 12.66 (99.23, 111.07)	105.55 ± 14.62 (98.71, 112.39)	103.55 ± 11.28 (98.27, 108.83)	105.95 ± 10.85 (100.72, 111.18)	0.39	0.82	0.57	10.57
	Reaction Time	88.00 ± 16.34 (80.35, 95.65)	90.60 ± 14.72 (83.71, 97.49)	92.15 ± 18.13 (83.66, 100.64)	96.16 ± 13.99 (89.42, 102.90)	0.14	0.37	0.94	19.70
	Complex Attention	95.10 ± 13.84 (88.62, 101.58)	95.70 ± 17.24 (87.63, 103.77)	100.75 ± 12.12 (95.08, 106.42)	105.42 ± 10.37 (100.42, 110.42)	0.31	0.04	0.44	14.01
	Cognitive Flexibility	94.35 ± 12.82 (88.35, 100.35)	100.45 ± 15.03 (93.42, 107.48)	100.20 ± 12.44 (94.38, 106.02)	105.00 ± 10.87 (99.76, 110.24)	0.01	0.17	0.67	14.42
	Processing Speed	105.20 ± 15.74 (97.83, 112.57)	107.70 ± 17.94 (99.30, 116.10)	107.05 ± 13.16 (100.89, 113.21)	109.26 ± 14.78 (102.14, 116.39)	0.19	0.70	0.96	14.35
	Executive Functioning	95.80 ± 12.40 (90.00, 101.60)	102.00 ± 14.23 (95.34, 108.66)	101.00 ± 11.92 (95.42, 106.58)	105.80 ± 10.34 (100.81, 110.77)	0.01	0.21	0.66	15.04
	Reasoning	102.37 ± 13.28 (95.97, 108.29)	109.55 ± 13.53 (103.23, 115.88)	102.39 ± 12.69 (96.08, 108.70)	104.63 ± 15.03 (97.39, 111.89)	0.03	0.57	0.28	18.09
	Simple Attention	95.30 ± 18.62 (86.59, 104.01)	88.70 ± 24.03 (25.71, 114.57)	97.30 ± 14.78 (90.38, 104.21)	104.53 ± 9.33 (100.03, 109.02)	0.95	0.04	0.07	29.82
	Motor Speed	103.05 ± 11.21 (97.80, 108.29)	100.86 ± 12.68 (77.45, 99.95)	99.50 ± 9.50 (95.05, 103.95)	100.47 ± 10.00 (95.65, 105.29)	0.64	0.45	0.44	12.02

Table 5.3. Means, standard deviations, and 95% confidences interval SAC, BESS, GSC, and VOMS outcomes at each session for ACTIVE training and non-training groups.

	Outcome	Non-training Group (n=20)		ACTIVE Training Group (n=20)		Adjusted *P* Value			80% RCI
		Session 1	Session 2	Session 1	Session 2	*Session*	*Group*	*Group X Session*	
SAC	Total Score	28.80 ± 1.28 (28.20, 29.40)	28.30 ± 1.17 (27.75, 28.85)	28.35 ± 1.76 (27.53, 29.17)	28.42 ± 1.43 (27.73, 29.11)	0.35	0.64	0.28	1.80
BESS	Total Score*	15.35 ± 6.29 (12.41, 18.21)	16.20 ± 9.38 (11.81, 20.59)	16.85 ± 6.46 (13.83, 19.87)	15.84 ± 7.78 (12.09, 19.59)	0.90	0.80	0.48	10.98
GSC	Total Symptom Score*	2.50 ± 3.03 (1.08, 3.29)	2.30 ± 4.84 0.04, 4.56)	5.10 ± 5.75 (2.41, 7.79)	1.89 ± 3.60 (0.10, 3.68)	0.02	0.40	0.04	6.19
VOMS	NPC Distance* (cm)	4.58 ± 4.67 (2.40, 6.77)	4.66 ± 4.82 (2.34, 6.98)	3.29 ± 1.74 (2.47, 4.10)	4.14 ± 2.02 (3.17, 5.11)	0.04	0.38	0.20	1.79
	*Lower scores indicate better performance								

CHAPTER 6

MANUSCRIPT 3

A brief aerobic training protocol in healthy subjects: The ACTIVE concussion management study

Introduction

There is a growing body of literature suggesting physiological disturbances in cerebral metabolism and blood flow [61] and sympathetic nervous system activity[65] following concussion, which consistently persist beyond clinical resolution.[61-63] Current concussion management guidelines suggest physical rest until asymptomatic [21,64] despite the fact that aerobic exercise may improve these physiological disturbances affected by concussion. Aerobic exercise following concussion has high clinical utility, with studies finding that individuals engaged in physical activity have reduced symptom burden, [6,66,67] increased cognition, [68] and decreased depression scores [68] compared to individuals undergoing rest following concussion. The literature surrounding this topic is small but largely in agreement about the benefit of exercise. However, these studies are generally completed in participants with a prolonged recovery and are limited by a number of factors including the failure to assess physiological changes or adaptations, such as maximal oxygen uptake and respiratory exchange ratio, resulting from the aerobic training.

Understanding the physiological mechanisms underlying clinical changes can have profound impact on establishing safe and effective exercise prescription guidelines following

concussion. Little is known about the body's ability to tolerate exercise acutely following concussion as traditional management guidelines advocate against physical activity. [21,64] Long-term aerobic training is known to improve cardiopulmonary responses, such as maximum oxygen consumption (VO_{2max}), respiratory exchange ratio, and lactate threshold, [19,206] but it is unknown if aerobic training applied over a duration that mimics the typically short concussion recovery window (~14 days) allows for acute and significant physiological adaptations. These data are critical first steps to establishing optimal frequency, duration, and intensity of training programs that can then be tested for concussion rehabilitation.

Exercise guidelines following concussion are currently nonexistent and little cardiopulmonary outcomes in response to exercise training have been established in acutely concussed individuals, which is necessary to understand the safety and effectiveness exercise interventions following concussion. The ACTIVE training intervention seeks to be first step in this process and is a Phase I clinical trial to determine how an aerobic training program designed for concussion rehabilitation affects healthy populations. Therefore, the primary purpose of this study was to determine the effect of a brief (6 training sessions administered in a two-week period) aerobic exercise program (acute concussion therapy intervention-ACTIVE training) that mimics the time window of concussion recovery on cardiopulmonary outcomes compared to a non-training group in a healthy, collegiate sample. We hypothesized ACTIVE training would significantly increase cardiopulmonary outcomes.

Methods

The methods of this study, particularly those in relation to the familiarization session, maximal cardiopulmonary exercise test (CPET), and training protocols, are described in detail in Teel XXXX. Briefly, recreationally active university students (30+ minutes of physical activity ≥3 days per week) individuals between the ages of 18-30 with no concussion history or other head injury within the past year, lower extremity injury preventing stationary bike cycling, or known cardiovascular health issues were recruited for this study. All participants received medical

approval by the study physician prior to enrollment and provided informed consent approved by the Institutional Review Board at the University of North Carolina at Chapel Hill (IRB #15-2387).

A parallel-group, unblinded randomized controlled trial was designed to assess the effect of ACTIVE training on cardiopulmonary outcomes in recreationally active university students. Participants were randomized into ACTIVE training or non-training (no intervention) groups upon study enrollment using a computer-generated sequence with block sizes of four. All participants completed an orientation session to become familiar with exercise equipment and testing protocols. Following orientation, participants completed two data collection sessions approximately 14 days apart. The time between data collection sessions best approximated concussion recovery times for the majority of collegiate athletes.[42]

Participants underwent a maximal cardiopulmonary exercise test (CPET) in a controlled laboratory setting at both data collection sessions for the determination of VO_{2max}. The CPET protocol can be found in **Table 6.1**. Cardiopulmonary outcomes were collected throughout the CPET using a ParvoMedics TrueOne® 2400 metabolic cart (ParvoMedics, Sandy, UT). Blood lactate (Lactate Plus lactate analyzer- Sports Resource Group, Hawthorne, NY) was collected three minutes following test completion. In order for the CPET to be considered a maximal test, at least three of the following criteria must be met: a) plateau in VO_2 defined as increase ≤ 2.1 ml/kg/min with an increase in exercise intensity at the test last stage, b) respiratory exchange ratio (RER) ≥ 1.10, c) rate of perceived exertion (RPE) ≥ 17, d) lactate ≥ 8.0mmol/L, and e) heart rate (HR) within 10 beats of age predicted heart rate max (220-age). Two of the 77 assessments (2.6%) did not meet the criteria for determination of a maximal exercise test and therefore were not included in the statistical analyses. A certified athletic trainer and a physician member of the research team were on call and prepared to respond during each CPET in case of an adverse event. The research team has over 20 years of experience conducting CPETs in healthy and clinical populations.

Between data collection sessions, participants in the ACTIVE training group completed

six 30-minute training sessions progressing from 60 to 80% of VO_{2max} achieved during the first CPET. To ensure the assigned exercise intensity was maintained, oxygen consumption levels were evaluated at the 5-, 15-, and 25-minute mark (3-minute recordings) during training sessions, with adjustments to workload occurring as needed. Participants in the non-training group received no intervention in the interim between data collection sessions. No changes to methods or participant recruitment were made throughout the trial and no guidelines to prematurely stop the trial were in place, as the study focused on young, active individuals.

Primary Outcomes

Cardiopulmonary outcomes measured via the metabolic cart were collected over 5-second intervals. Maximal oxygen uptake and respiratory exchange ratio were calculated as the average of the three highest readings from the last 30 seconds prior to termination of each CPET. Maximum heart rate was the highest heart rate value recorded throughout the exercise protocol. Predicted maximal heart rate was calculated using the 220-age formula. Ventilatory threshold was calculated using the V-slope method.[207] Blood lactate was evaluated with a finger prick using a mobile lactate analyzer.

Statistical Analysis

All statistical analyses were completed in SAS (Version 9.4; SAS Institute, Inc., Cary, North Carolina). Descriptive analyses were completed for all primary outcomes. Intention-to-treat analyses were performed; results were analyzed based on the randomized assignment regardless of participant adherence. To determine the effect of ACTIVE training on cardiopulmonary outcomes, separate 2 (group) by 2 (session) ANOVAs were run. Demographics and primary outcomes at the first test session did not differ between groups; therefore, no covariates were added to any statistical model. Means were trimmed using a 10% winsorized method to temper the effect of outliers without reducing sample size.[197] A priori alpha was set to 0.05. For all outcomes, 80% reliable change indices (RCIs) were calculated to determine clinical relevance between any potential mean differences. A power analyses

(G*Power Version 3.1, Düsseldorf, Germany) determined that 36 participants (18 per group) were needed for this study. Forty participants were recruited to account for potential attrition.

Results

Participants were recruited and tested between August 2016 and March 2017. Forty-five individuals were screened for participation, with forty participants meeting the inclusion criteria and enrolling into the study. No participants were lost to follow up throughout the study period. Baseline participant characteristics can be found in **Table 6.2**. No significant group differences in any demographic variable were observed.

Participants were evenly randomized into ACTIVE training (n=20) and non-training (n=20) groups. Most participants (n=12, 60%) completed all six training sessions over the two-week interval and all participants completed at least four training sessions. Missed sessions for those with only four sessions (n=2) were due to illness. Three of the ten missed sessions were caused by an unforeseen university closure that prevented researchers and participants from accessing the laboratory.

There were no adverse events reported during the CPETs or exercise training sessions. One participant (2.5%) fainted during a blood draw, but syncope is a known risk occurring in approximately 5% of individuals during venipuncture.[208] Our study team expected this to occur and was prepared to accommodate this participant. Three (3.6%) CPETs were missed throughout the study, due to the participant fainting during the preceding venipuncture (n=1) and calibration issues associated with software malfunctions of the computer connected to the metabolic cart (n=2). Two of the 77 completed assessments (2.6%) did not meet the criteria for determination of a maximal exercise test and were removed from subsequent statistical analyses, indicating a high level of adherence to the maximal exercise protocol.

Six intervention participants reached a higher subsequent stage and none finished at a lower stage during the second CPET, compared to five participants improving and five participants declining in CPET stage for the non-training group. VO_{2max} (t_{33}=2.25, P=0.031),

maximal heart rate (t_{32}=3.72, *P*<0.001), percent of estimated maximal heart rate (t_{32}=3.71, *P*=0.008), rate of perceived exertion (t_{31}=3.37, *P*=0.002), test duration (t_{33}=3.36, *P*=0.002), and VO_2 at ventilatory threshold (t_{33}=2.89, *P*=0.007) were significantly greater during the second CPET compared to the first one (**Table 6.3**). A main effect of group was observed for rate of perceived exertion (t_{38}=2.89, *P*=0.006), with the intervention group reporting higher values during their CPETs. A significant overall interaction was present for percentage of VO_{2max} at which the ventilatory threshold occurred ($F_{1,33}$=5.98, *P*=0.02), with the intervention group significantly improving at the second CPET. No other overall interaction effects were significant for any outcome; however, post hoc analyses revealed that the intervention group had significantly improved heart rate (t_{32}=3.27, *P*=0.01), percentage of predicted maximal heart rate (t_{32}=3.26, *P*=0.01), test duration (t_{33}=2.96, *P*=0.03), and VO_2 at ventilatory threshold (t_{33}=3.13, *P*=0.018) outcomes at the second CPET.

Discussion

The intervention group had significantly improved outcomes at the second CPET, suggesting ACTIVE training was effective in improving cardiopulmonary outcomes in healthy participants. This provides an important proof of concept that concussed patients could potentially follow the same pattern of observed changes seen in this group of healthy university students. Physiological deficits, such as cerebral metabolism and blood flow [61] and sympathetic nervous system activity[65], are being reported more frequently following concussion and novel diagnostic and management techniques are being evaluated for their clinical utility. Exercise as concussion rehabilitation is gaining clinical traction but little evidence about how acute exercise may influence physiological outcomes exists. Therefore, a thorough investigation of the expected physiological adaptations resulting from a brief aerobic exercise-training program is necessary to lay the foundation for future works in concussed individuals.

Main effects of session for cardiopulmonary outcomes were noted, with improved performance at the second CPET. A closer inspection of the data indicated the intervention

group drove these changes, as the non-training group did not significantly improve between test sessions for any cardiopulmonary outcomes. Most improvements seen in the intervention group exceeded the measurement error associated with any assessment tool used in this study[53] and some variables improved beyond the calculated reliable change indices, suggesting true training effects. Improvements in neuromuscular efficiency, through motor unit firing and recruitment, likely explain the cardiopulmonary changes measures in this study, particularly as our participants were not trained cyclists.[209] The increased test duration, increased wattage at CPET termination, and lack of change in RER outcomes further support that neuromuscular, not metabolic, adaptation are driving cardiopulmonary improvements.

ACTIVE training provided six training sessions over a two-week window to best approximate clinical concussion recovery timelines and typical rehabilitation schedules. The intervention progressed from 60-80% of VO_{2max}, following ACSM exercise prescription guidelines. Previous research has recommended that exercise training protocols last for at least 6-8 weeks [47] and that training intensities of 80-100% of VO_{2max} provide largest improvements in aerobic capacity.[46] The short duration and moderate intensity of ACTIVE training was still sufficient to produce cardiopulmonary changes and the more conservative training protocol is less likely to exacerbate concussive symptoms, providing higher clinical utility for acute concussion rehabilitation. Concussed athletes, particularly those experiencing prolonged recovery, may spend considerable time away from physical activity when managed with current clinical recommendations of rest. The cardiopulmonary improvements and neuromuscular efficiency adaptations seen following ACTIVE training provides evidence that exercise training may help athletes safely prevent the loss of physical conditioning during recovery, a common fear post-concussion.[210]

The concussion literature describing aerobic exercise interventions focuses primarily on symptoms outcomes following rehabilitation.[14,58,66] The few studies that describe physiological outcomes during or following exercise interventions focus on heart rate, blood pressure, and

duration of the exercise bout. The exercise mode (treadmill vs. bike) and progression schedule used during CPETs varies widely in the concussion literature,[6,67] making comparison between ACTIVE training test duration and those reported in other studies difficult. The maximal heart rate achieved during the CPET in this study is similar to those reported in concussed individuals following exercise therapy (179 ± 17 bpm).[6] The changes in heart rate and test duration from pre to post-exercise intervention are much greater in concussed participants;[6,67] however, this is due to lower values recorded during the first CPET session because of symptom exacerbation. To the best of our knowledge, no aerobic exercise interventions have described changes in respiratory exchange ratio, blood lactate, and ventilatory threshold in the concussion literature.

The benefits of aerobic exercise outweigh the potential risks in healthy, young individuals. No adverse events were reported in conjunction with physical activity throughout this study and potential benefits of aerobic exercise include reduced risk of cardiovascular disease,[202] obesity,[211] and high blood pressure,[212] although not directly assessed in this study. The ACTIVE training intervention was designed to target the physiological domains that may be impaired following concussion as a method of improving recovery and not as a method of improving aerobic capacity. However, the cardiopulmonary improvements in the intervention group may have important translations in concussed populations, as it may allow concussed participants to maintain fitness levels, or at least minimize physical deconditioning, during recovery. Beyond physiological benefits, aerobic exercise can improve mental health by reducing depression[213] and anxiety.[214] These benefits may be additionally beneficial for concussed participants as mood changes, social isolation, and fear of detraining can negatively affect mental health following concussion.[210,215] ACTIVE training should be tested in a group of acutely concussed individuals to better understand the intervention's effect on psychological outcomes.

Limitations

This study implemented six training sessions over a two-week period to best approximate typical concussion recovery times. However, the high degree of variability in concussion recovery may cause individuals to have considerably shorter or longer training periods than used in this study, which may influence the ability to compare outcomes to those presented in this study. This study used recreationally active students. Highly trained athletes may show less change in cardiopulmonary responses due to their already high fitness capacity. Future research should evaluate the effects of aerobic training programs on youth and elite athlete cohorts to determine if they respond differently to healthy, recreationally active collegiate athletes.

Tables

Table 6.1. Protocol for the CPET.

Cardiopulmonary Exercise Test	
0:00	Begin pedaling at 50W workload
2:00	Workload increased to 100W
4:00	Workload increased to 150W
6:00	Workload increased to 180W
8:00	Workload increased to 210W
10:00	Workload increased to 240W
Every minute following, workload increased by 30W	
Termination- Volitional fatigue	

Table 6.2. Demographic characteristics for all participants. No significant group differences were observed.

Variable	Non-Training Group (n=20)	ACTIVE Training Group (n=20)	Adjusted P-Value
Age	21.2 ± 2.7	20.4± 1.1	0.25
Sex	10 male, 10 female	10 male, 10 female	1.00
Height (cm)	174.3 ± 9.1	173.5 ± 11.4	0.81
Weight (kg)	71.7 ± 11.1	71.2 ± 12.8	0.98
Self-Perceived Fitness	4.1± 0.6	3.8 ± 0.6	0.07
Premorbid Conditions (self)	4	5	0.46
Premorbid Condition (family)	7	9	0.52
No. Previous Concussions	0.55 ± 1.10	0.27 ± 0.55	0.35

Table 6.3. Means, standard deviations, 95% confidence intervals, and 80% RCIs for all cardiopulmonary outcomes.

Outcomes	**Non-training Group (n=20)**		**ACTIVE Training Group (n=20)**		**Adjusted *P* Value**			**80% RCI**
	Session 1	*Session 2*	*Session 1*	*Session 2*	*Group*	*Session*	*Group * Session*	
Maximal Oxygen Uptake (ml/kg/min)	42.9 ± 8.44 (39.0, 46.9)	43.8 ± 9.6 (39.2, 48.5)	46.2 ± 9.5 (41.6, 50.7)	48.4 ± 10.2 (43.1, 53.6)	0.32	0.03	0.84	4.29
VO_2 at Ventilatory Threshold	28.0 ± 5.8 (25.3, 30.7)	28.1 ± 6.9 (24.8, 31.6)	**27.9 ± 7.4 (24.3, 31.5)**	**30.9 ± 7.1 (27.2, 34.5)**	0.73	<0.01	0.09	2.96
Ventilatory Threshold % of VO_{2max}	65.5 ± 7.7 (61.9, 69.1)	64.0 ± 6.2 (61.0, 67.0)	60.4 ± 7.5 (56.8, 64.0)	64.9 ± 10.1 (59.6, 70.2)	0.38	0.25	0.02	7.44
Respiratory Exchange Ratio	1.16 ± 0.07 (1.12, 1.19)	1.16 ± 0.06 (1.13, 1.19)	1.16 ± 0.06 (1.14, 1.19)	1.16 ± 0.06 (1.13, 1.19)	0.88	0.79	0.89	0.08
Maximal Heart Rate (beats per minute)	181 ± 11 (175, 186)	184 ± 10 (178, 189)	181 ± 9 (177, 185)	187 ± 8 (183, 191)	0.71	<0.01	0.32	7.19
Duration of Test (MM:SS)	9:40 ± 2:38 (8:26, 10:54)	9:42 ± 2:38 (8:27, 10:57)	10:18 ± 2:52 (8:55, 11:42)	10:38 ± 3:01 (9:05, 12:11)	0.99	<0.01	0.34	00:42
Workload at Test Completion (Watts)	236 ± 54 (210, 261)	235 ± 59 (207, 263)	253 ± 71 (218, 287)	261 ± 76 (222, 300)	0.33	0.08	0.44	20.43
Rate of Perceived Exertion	17.8 ± 1.3 (17.2, 18.5)	18.5 ± 1.3 (17.9, 19.1)	18.7 ± 1.3 (18.1, 19.3)	19.4 ± 1.0 (18.9, 19.9)	<0.01	<0.01	0.53	1.27
Blood Lactate at Test Completion (mmol/L)	12.5 ± 3.9 (10.2, 14.9)	12.1 ± 2.6 (10.7, 13.5)	12.5 ± 3.6 (10.5, 14.6)	12.5 ± 2.2 (11.1, 14.0)	0.87	0.99	0.88	3.76
% of Predicted Maximal Heart Rate	90.8 ± 5.2 (88.4, 93.3)	92.2 ± 5.1 (89.6, 94.7)	90.6 ± 4.7 (88.3, 92.9)	93.6 ± 4.1 (91.5, 95.8)	0.87	<0.001	0.31	6.07

CHAPTER 7

MANUSCRIPT 4

A randomized controlled trial investigating the effect of aerobic exercise training on electroencephalography in healthy participants: The ACTIVE concussion management study

Introduction

Traumatic brain injuries are a serious public health concern costing the healthcare system over $60 billion per year,[216] with concussions representing the most common form of traumatic brain injury.[194] Concussions can cause a number of functional deficits, including symptom, cognitive, balance, and visual dysfunction.[64] Due to these deficits and the lack of abnormal findings on standard neuroimaging tools such as CT and MRI scans, concussions were originally described as a functional and non-structural injury.[21] While more recent research has increasingly associated concussion with structural deficits, many of these neuroimaging techniques are limited by their high cost and lack of portability. Electroencephalography (EEG) has a well-documented history in detecting alterations in brain-injured subjects, is relatively cheap and easy to administer, and evaluates the underlying neural processes contributing to functional networks, making them a sensitive and appropriate tool to evaluate concussive effects.[157]

Concussions are believed to affect connectivity between neurons, disrupt reticular system activation, and alter function in thalamo-cortical tracts.[161] As such, power analyses are among the most sensitive electrophysiological measures to detect changes after concussion.[157,161,162] These alterations are reflected in the literature, which shows that

concussion decreases peak/average alpha power[73,75,163,164] and alpha-theta ratio.[73] These neural markers are tied to attention and memory domains,[217] which are commonly impaired following concussion.[115] More recent studies investigating EEG during clinical concussion assessments have found hemispheric differences, with concussed patients displaying power asymmetries between left and right sides.[169-171]

Clinical concussion care continues to change in response to new evidence for diagnosis and management. Traditional management guidelines have advocated for complete physical rest until associated symptoms have dissipated.[64] However, emerging evidence suggests no benefit to strict rest, with some studies finding that complete rest prolongs recovery.[12,105] In response, clinicians and researchers have begun to develop active rehabilitation strategies, including visual, vestibular, and dual-task paradigms. Aerobic exercise training has emerged as a promising therapeutic area, with studies finding improved recovery times and decreased symptom presence in exercised vs. non-exercised patients.[5,6,67,68,71] While the work in this area has mostly focused on individuals in chronic (4+ weeks) recovery stages,[5,6,68,71] more studies continue to evaluate the benefits of exercise acutely following concussion, with no serious adverse reported.[57]

As the acute management of sport-related concussion continues to evolve, more active treatments, such as aerobic exercise, are being incorporated into clinical management and it is unknown how these rehabilitation paradigms may influence other concussion management tools, including EEG. As EEG outcomes are known to change over the course of clinical concussion recovery,[169-171] it is difficult to tease out the effect of exercise from the effect of recovery in this population. Therefore, it is essential to understand how exercise may influence EEG outcomes in non-injured populations to minimize confounding factors. While EEG outcomes are affected during a bout of exercise[44,45] and in chronic exercise training in clinical populations,[29] little is known about the way that aerobic training influences resting-state EEG outcomes in healthy populations. Therefore, the primary purpose of this study is to determine if

a brief aerobic training protocol designed for use in concussion management influences spectral resting-state EEG outcomes in a group of healthy, active participants. We hypothesized that there would be no changes in any EEG outcomes due to the brief nature of the training program.

Methods

Participants

Recreationally active participants between the ages of 18-30 years were recruited for this study. Participants were excluded if they had a history of head trauma within the past year, lower extremity injury that would prevent exercise training, any known cardiovascular abnormalities, or recreational drug use. The study physician provided medical clearance to all participants prior to enrollment. Participants provided informed consent approved by the University's Institutional Review Board.

Procedures

A parallel-group randomized controlled trial was designed to assess the effect a brief exercise training protocol on resting-state EEG outcomes in healthy participants. Participants were randomized into either an aerobic training, ***a***cute ***c***oncussion ***t***herapy ***i***nter***ve***ntion (ACTIVE intervention), or non-training (no intervention) groups upon study enrollment using a computerized-generated randomization sequence with block sizes of four. All participants completed a maximal exercise test in a controlled laboratory setting on a Lode stationary electric-brake bike (Lode, Gronigen, The Netherlands), with vital signs assessed prior to and following the exercise. Maximal oxygen uptake at the termination of testing was used to create individualized workout intensities for participants assigned to the aerobic training group.

All participants completed two, resting-state EEGs and psychological scale assessments 10-14 days apart. ACTIVE training participants completed six 30-minute exercise sessions between EEG sessions. Exercise intensity progressed from 60 to 80% of maximal oxygen consumption reached during the maximal exercise test over the course of the training sessions

and this progression follows the exercise prescription guidelines set forth by the American College of Sports Medicine. To ensure appropriate exercise intensities were sustained throughout each training session, oxygen consumption levels were checked at the 5-, 15-, and 25-minute mark (3-minute recordings). Non-training participants received no intervention between EEG sessions. More details regarding the exercise intervention can be found elsewhere (Teel XXXX).

The lead author was responsible for study enrollment, the allocation of randomization, and supervised all study activities. Maximal exercise testing and aerobic training protocols were supervised by an experienced exercise physiologist with over 20 years experience working in exercise prescription in clinical populations. An EEG expert, publishing in the field for over 15 years, assisted with the EEG procedures and analysis. Neither the research investigators nor participants were blinded to the intervention; however, the EEG expert and study biostatistician were blinded to group assignment. No changes to methods or subject recruitment occurred following trial initiation. As this study focused on healthy, recreationally active participants, no guidelines to prematurely stop the trial were implemented.

EEG Procedures

A Brain Products (Munich, Germany) EEG System continuously recorded data using a 16-channel actiCAP system, with integrated noise subtraction circuits, and a BrainVision V-Amp amplifier. Raw data was recorded at a sampling rate of 500 Hz and data were referenced to a central electrode. The electrodes were spaced using the traditional 10-20 system and impedance for all channels was kept below 5 kΩ. All EEG recordings took place in a quiet, dimly lit room. Each participant complete four conditions: seated eyes open, seated eyes closed, standing eyes open, and standing eyes closed. All conditions lasted for two minutes.

Prior to statistical analysis, all EEG recordings were processed to remove any extraneous artifact, Bad channels were visually identified and an interpolation by spherical spline correction method was applied. The first ten seconds and last ten seconds from all EEG

recordings were removed to assist in cleaning the data. Channels were re-referenced to the common average of all electrodes and data was filtered between 0.5-59Hz. ICA-based ocular artifact correction was applied to remove any eye blinks or eye movements. Data was re-sampled to 256Hz and continuous data was segmented into 2-second epochs. Each 2-second epoch was manually inspected for any artifact not removed by previous steps and any bad epochs were removed, with participants eliminated from statistical analysis if more than 25% of their epochs were removed. All clean, 2-second epochs were averaged together and a Fast Fourier Transform (FFT), normalized to the total value of the segment, was applied with a Hanning window 10% in length. Conditions were collapsed to reduce contrasts among seated/standing conditions to create two EEG conditions of interest: eyes open conditions and eyes closed conditions. Individual channel data was also collapsed into frontal, central, and posterior regions of interest (ROI). Mean power for alpha and theta frequency band, alpha/theta ratio, and peak alpha power for each EEG condition and ROI were the outcomes of interest derived form the FFT.

Psychological Scales

GAD-7. The Generalized Anxiety Disorder-7 Scale (GAD-7) is a global measure of anxiety. The GAD-7 contains seven questions related to nervousness, worry, relaxation, and mood. Participants are asked to rate how often they experienced those feelings (not at all, several days, more than half the days, or nearly every day) over the preceding two weeks. A total score ranging from 0-21 will be calculated for the GAD-7, with higher scores indicative of greater anxiety levels. Score of 10 or greater may represent clinically significant findings. The psychometric properties of the GAD-7, including its validity, are well reported in the literature.[218,219]

PHQ-9. The Patient Health Questionnaire-9 Scale (PHQ-9) is a global measure of depression. Similar to the GAD-7, participants are given nine questions regarding negative feelings and behaviors and are asked to rate how often they experienced those feelings over

the preceding two weeks. A total score ranging from 0-27 was calculated for the PHQ-9, with higher scores indicating greater levels of depression. A score of 10 or greater may be indicative of clinically meaningful levels of depression. The PHQ-9 is a valid psychological tool.[220,221]

Statistical Analyses

All statistical analyses were completed in SAS (Version 9.4; SAS Institute, Inc., Cary, North Carolina). Descriptive analyses were completed for all primary outcomes. Intention-to-treat analyses were performed, meaning that groups were analyzed based on the randomized assignment received upon enrollment regardless of protocol adherence. Group (2) by session (2) mixed-model ANOVAs were conducted to evaluate the effect of ACTIVE training on all EEG variables of interest. No covariates were added to any statistical model, as there were no group differences between demographic variables. To evaluate test-retest reliability, $ICC_{2,k}$ outcomes were calculated as seated and standing conditions were collapsed for analysis. In addition, 80% reliable change indices were calculated to determine the EEG stability. A priori alpha was set to 0.05. Sample size was determined using a power analysis conducted in G*Power (Version 3.1, Düsseldorf, Germany) and it was determined that 36 participants (18 per group) were need for this study. Forty participants were to account for potential attrition throughout the study.

Results

Forty participants were retained throughout the study period and completed the full protocol between August 2016 and March 2017. Participants were randomized into the ACTIVE training or non-training groups upon study enrollment, with an equal number of males (n=10) and females (n=10) in each group. Age, height, weight, concussion history, or premorbid conditions were not significantly different between groups ($p>0.25$). Six participants had data removed (5 participants for one session only, 1 participant for both sessions) removed from analysis after EEG processing because of excess artifact due to motion, leaving 34 participants with usable EEG data from both sessions. Separate 2 (group) by 2 (session) mixed-model

ANOVAs were conducted to determine main effects and interactions of group and session. Separate tests were performed on mean alpha and theta power, alpha/theta ratio, and peak alpha power (in Hz) in frontal, central, and posterior ROIs during eyes open and eyes closed conditions.

Eyes Open Conditions: Main effects of session were observed for mean alpha power for all ROIs (Frontal: $F_{1,32}$=7.43, p=0.01; Central: $F_{1,32}$=9.32, p=0.005; Posterior: $F_{1,32}$=4.88, p=0.03) during the eyes open conditions (**Figure 7.1**), with higher mean alpha values at the second test session. The intervention group had significantly increased mean alpha power from session 1 to session 2 ($t_{(32)}$= -2.89, p=0.03), although the overall interaction term failed to reach statistical significance. Both groups had significantly increased peak alpha in the posterior ROI at the second test session ($F_{1,32}$=4.57, p=0.04), but no group or interaction effects were noted for peak alpha. ACTIVE training had no main or interaction effects on mean theta power or alpha/theta ratio (**Table 7.2**).

Eyes Closed Conditions. Significant findings for eyes closed conditions were only present only in the central ROI for mean alpha and theta power. Central theta was significantly higher in the intervention group compared to the non-training group ($F_{1,37}$=5.59, p=0.02). A significant overall interaction was observed for central alpha power ($F_{1,32}$=6.45, p=0.016), with the intervention group displaying significantly increased mean alpha power between test sessions relative to non-training participants ($t_{(32)}$= -3.57, p=0.006). No other significant main effects or interactions were observed during eyes closed conditions (**Figure 7.2 & Table 7.2**).

Psychological Scales. All participants reported sub-clinical levels of anxiety and depression at both time points, with no subjects meeting the criteria for clinical referral (total score >10) for either scale. ACTIVE training participant reported higher levels of improvement on the GAD-7 (ACTIVE: -1.26 ± 2.16; Non-training: -0.93 ± 1.91; p=0.68) and PHQ-9 (ACTIVE: -0.47 ± 1.81; Non-training: -0.07 ± 1.47; p=0.68) between test sessions, although these results did not reach statistical significance. Changes in mean alpha was moderately correlated to

change in GAD-7 (ACTIVE: *r*=-0.42, p=0.07; Non-training: *r*=0.07, p=0.79) and PHQ-9 (ACTIVE: *r*=-0.41, p=0.07; Non-training: *r*=0.08, p=0.78) scores for the invention group, but no relationship between mean alpha and psychological scales were observed for the non-training group.

Reliability. Test-retest reliability was evaluated using the $ICC_{2,k}$ method and groups were collapsed for this analyses due to the general lack of significant group differences found in the mixed-model analysis. Reliability outcomes ranged from poor ($ICC_{2,k}$=0.311) to excellent ($ICC_{2,k}$=0.903) depending the EEG outcome of interest. Mean alpha power had the highest reliability (0.815< $ICC_{2,k}$), with all ROIs and conditions displaying excellent levels of reliability. Overall, EEG outcomes had good to excellent reliability (0.600< $ICC_{2,k}$) with the exception of mean theta power, which had low-to-moderate reliability (0.311< $ICC_{2,k}$<0.571). No discernable pattern was detected across the ROIs; reliability varied widely within frontal, central, and posterior ROIs depending on the variable of interest. Over the 24 EEG outcomes of interest, 3 (13%) had low reliability ($ICC_{2,k}$<0.4), 8 (33%) had moderate reliability (0.4≤ $ICC_{2,k}$<0.7), and 13 (54%) were highly reliable (0.7≤ $ICC_{2,k}$). All reliability results can be found below in **Tables 7.1 & 7.2**.

Discussion

The intervention group displayed significantly increased mean alpha power in central regions of interest during both the eyes open and eyes closed conditions following ACTIVE training, which was not observed in the non-training group. The intervention group also had significantly higher mean theta power in the central ROI. The increased mean alpha power in response to ACTIVE training is opposite to trends following concussion, as alpha power has been consistently show to decrease following injury.[73,164] Still, little consistency in EEG-related biomarkers of concussion is found in the literature and almost no studies have evaluated the effect of exercise training on EEG outcomes in healthy participants. Concussion management continues towards earlier and more active forms of rehabilitation, including aerobic exercise.

Therefore, investigating the effect of a brief aerobic training program designed for future use in concussed populations can have important implications for understanding the neural underpinning of change caused by clinical rehabilitation programs, such as exercise training programs.

ACTIVE training significantly increased mean alpha power in both eyes open and eyes closed conditions, particularly in the central ROI. The intervention group also had significantly higher mean theta values than the non-training group in the central ROI. Few findings were elicited during the eyes closed conditions, but large increases in alpha power during eyes closed conditions[222] may have masked other findings. Previous literature has shown alpha and theta power related to positive (meditative states[223]) and negative (anxiety and depression[224,225]) psychological states and aerobic exercise is known to decrease anxiety[214] and depression.[213] No previous studies have investigated EEG changes following aerobic training in healthy cohorts, but EEG changes have been elicited following aerobic training in depressed patients.[29] The change in mean central alpha found in this study correlated to both the GAD-7 and PHQ-9 for intervention participants only. This may indicate a neuroprotective effect of exercise through enhanced psychological well-being, which should be investigated further in future studies.

EEG outcomes, particularly mean alpha power, had good to excellent reliability ($ICC_{2,k}$<0.600) with the exception of mean theta power, which had low to moderate reliability (0.311< $ICC_{2,k}$<0.571). No pattern in reliability outcomes between ROIs or conditions could be discerned. Previous studies evaluating spectral EEG show that outcomes are highly reliable.[226-229] Our findings are in mixed agreement with the current literature. Alpha and alpha/theta ratios had excellent reliability, in agreement with previous studies, but the low to moderate reliability of mean theta power was in contrast to previous findings and limits its clinical utility. However, previous studies focus mainly on mean power during seated conditions only and do not report reliability using intra-class correlation coefficients, which limits our ability for direct comparison.

The ACTIVE training protocol is an aerobic exercise protocol designed for future use in concussion rehabilitation and, as such, EEG markers of interest were chosen for their application to both traumatic brain injury and exercise fields. Alpha and theta power in particular are heavily tied to attention and memory, which are known to be disrupted following concussion,[230,231] and have been linked to associated clinical diagnoses such as Alzheimer's Disease.[217,232] Exercise has been shown to increase hippocampal volume [142,143] and increase cerebral blood volume [143] to the hippocampus. These brain areas are heavily tied to cognition, and are implicated in a number of top-down processing domains including memory, spatial awareness, and attention.[144] Additionally, the preliminary data correlating EEG outcomes to psychological scales may be an important finding for future work in concussed populations, as negative psychological outcomes following concussion have been previously reported.[215] EEG biofeedback targeting alpha and theta oscillations has also proven to be effective in rehabilitating cognitive deficits in traumatic brain injury populations,[172,233] so these biomarkers may represent a potential treatment in addition to their utility in concussion diagnosis.

Limitations

This study is limited by a number of factors. This study implemented six training sessions over a two-week period to best approximate typical concussion recovery times. This brief training window may not be robust enough to provide neural adaptation that can be evaluated via EEG. When translating these results to concussed individuals, the high degree of variability in concussion recovery may cause individuals to have considerably shorter or longer training periods than used in this study, which may influence the ability to compare outcomes to those presented in this study. We were unable to conduct source localization analyses due to the small array of electrodes used, but future studies should explore the relationship between EEG, exercise, and clinical outcomes using denser electrode arrays. There is a high degree of variability of in EEG markers of interest in both the concussion and exercise literature. Other biomarkers may have yielded different results. Concussive symptoms and deficits are variable

in nature, but future studies should explore the relationship between EEG outcomes and concussive deficits at an individual level.

Conclusions

EEG has not been thoroughly studied in the concussion literature or in the exercise literature in healthy populations. Concussion rehabilitation is increasingly using aerobic exercise as a therapeutic intervention, but the influence this may have on EEG biomarkers, even in healthy populations, remains unknown. Mean alpha power was significantly increased following ACTIVE training. The change in mean alpha was moderately correlated to psychological improvements in the intervention group, while no relationship between EEG and psychological outcomes were assessed in the non-training group. EEG outcomes generally showed good to excellent reliability under all conditions and ROIs, with the exception of mean theta power that showed low to moderate reliability. Future studies should more thoroughly evaluate the relationship between ACTIVE training, neurophysiological, and psychological outcomes as well as the deficit and subsequent recovery of EEG biomarkers following acute concussion.

Figures

Figure 7.1. Mean power results for alpha findings during eyes open conditions. A significant main effect of session was found for each region of interest.

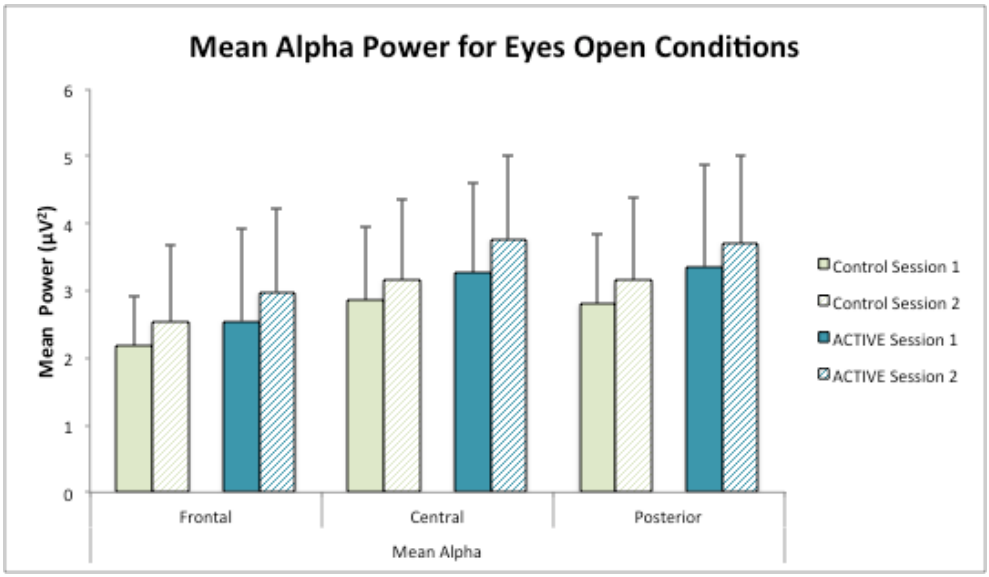


Figure 7.2. Mean power results for alpha and theta findings in the central ROI during eyes closed conditions. Main theta power was significantly increased at the second session for both groups, with the intervention group had significantly increased mean alpha between sessions compared to the non-training group.

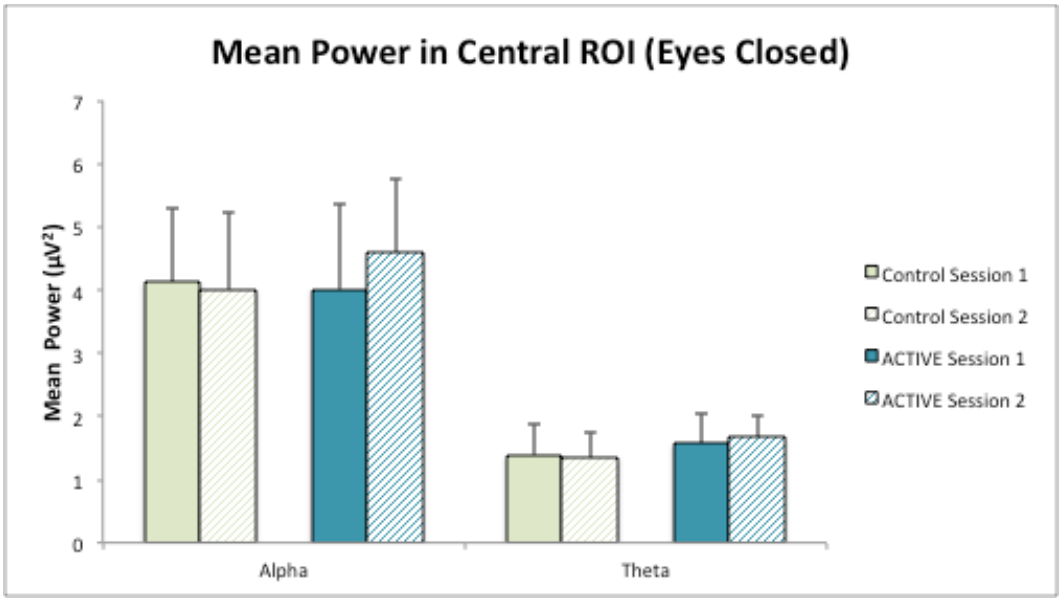


Table 7.1. Means, standard deviations, 95% confidence intervals, and 80% RCIs for all EEG outcomes during eyes open conditions.

Eyes Open Conditions	Non-training Group (n=20)		ACTIVE Training Group (n=20)		*P* Value			$ICC_{2,k}$	80% RCI
	Session 1	Session 2	Session 1	Session 2	*Session*	*Group*	*Session X Group*		
Alpha Mean Power (μV^2)									
Frontal	2.17 ± 0.74 (1.78, 2.57)	2.54 ± 1.14 (1.97, 3.10)	2.55 ± 1.38 (1.91, 3.20)	2.98 ± 1.24 (2.83, 3.58)	0.01	0.33	0.83	.866	0.80
Central	2.85 ± 1.10 (2.26, 3.43)	3.15 ± 1.20 (2.55, 3.75)	3.27 ± 1.34 (2.64, 3.90)	3.77 ± 1.24 (3.17, 4.37)	0.005	0.18	0.43	.901	0.85
Posterior	2.81 ± 1.02 (2.27, 3.35)	3.15 ± 1.23 (2.54, 3.76)	3.36 ± 1.52 (2.65, 4.06)	3.70 ± 1.31 (3.07, 4.32)	0.03	0.24	0.98	.903	0.84
Theta Mean Power (μV^2)									
Frontal	1.99 ± 0.53 (1.70, 2.28)	1.81 ± 0.59 (1.51, 2.10)	1.81 ± 0.54 (1.56, 2.06)	1.87 ± 0.45 (1.65, 2.09)	0.64	0.75	0.31	.324	0.19
Central	1.84 ± 0.57 (1.54, 2.15)	1.82 ± 0.55 (1.55, 2.09)	1.71 ± 0.48 (1.48, 1.94)	1.75 ± 0.38 (1.57, 1.94)	0.83	0.48	0.75	.571	0.40
Posterior	1.68 ± 0.33 (1.51, 1.86)	1.58 ± 0.47 (1.35, 1.81)	1.71 ± 0.50 (1.48, 1.94)	1.57 ± 0.23 (1.46, 1.68)	0.16	0.89	0.82	.394	0.25
Alpha/Theta Ratio									
Frontal	1.26 ± 0.57 (0.95, 1.56)	1.76 ± 1.35 (1.09, 2.44)	1.72 ± 1.27 (1.13, 2.31)	1.75 ± 0.82 (1.36, 2.15)	0.23	0.61	0.25	.649	0.48
Central	1.85 ± 1.05 (1.28, 2.41)	1.95 ± 1.07 (1.42, 2.49)	2.20 ± 1.24 (1.62, 2.79)	2.45 ± 1.05 (1.95, 2.96)	0.28	0.21	0.60	.877	0.78
Posterior	1.89 ± 1.82 (1.45, 2.33)	2.49 ± 1.79 (1.61, 3.38)	2.35 ± 1.43 (1.68, 3.02)	2.61 ± 1.09 (2.09, 3.14)	0.08	0.55	0.45	.705	0.56
Peak Alpha Power (Hz)									
Frontal	9.78 ± 0.84 (9.33, 10.23)	9.94 ± 0.64 (9.63, 10.26)	9.70 ± 0.78 (9.33, 10.06)	9.90 ± 0.67 (9.58, 10.22)	0.18	0.65	0.99	.567	0.41
Central	10.08 ± 0.73 (9.69, 10.47)	10.35 ± 0.57 (10.07, 10.63)	10.04 ± 0.69 (9.72, 10.36)	10.07 ± 0.72 (9.73, 10.42)	0.22	0.38	0.38	.582	0.42
Posterior	10.06 ± 0.71 (9.68, 10.43)	10.29 ± 0.62 (9.99, 10.60)	9.92 ± 0.61 (9.63, 10.20)	10.10 ± 0.74 (9.74, 10.45)	0.04	0.31	0.75	.786	0.67

Table 7.2. Means, standard deviations, 95% confidence intervals, and 80% RCIs for all EEG outcomes during eyes closed conditions.

Eyes Closed Conditions	Non-training Group (n=20)		ACTIVE Training Group (n=20)		*P* Value			$ICC_{2,k}$	80% RCI
	Session 1	Session 2	Session 1	Session 2	*Session*	*Group*	*Session X Group*		
Alpha Mean Power (μV^2)									
Frontal	3.46 ± 1.23 (2.80, 4.11)	3.43 ± 1.42 (2.72, 4.14)	3.44 ± 1.64 (2.67, 4.21)	3.65 ± 1.19 (3.08, 4.23)	0.68	0.91	0.70	.852	0.75
Central	4.13 ± 1.15 (3.52, 4.74)	4.01 ± 1.35 (3.33, 4.68)	4.01 ± 1.22 (3.44, 4.58)	4.60 ± 1.15 (4.04, 5.15)	0.03	0.56	0.02	.889	0.82
Posterior	4.72 ± 1.53 (3.90, 5.54)	4.46 ± 1.42 (3.76, 5.17)	4.57 ± 1.51 (3.87, 5.28)	4.59 ± 1.12 (4.05, 5.13)	0.37	0.81	0.67	.879	0.79
Theta Mean Power (μV^2)									
Frontal	1.69 ± 0.58 (1.38, 2.00)	1.61 ± 0.56 (1.33, 1.89)	1.84 ± 0.46 (1.63, 2.06)	1.91 ± 0.42 (1.71, 2.11)	0.94	0.10	0.40	.311	0.48
Central	1.72 ± 0.62 (1.39, 2.05)	1.55 ± 0.58 (1.31, 1.79)	1.74 ± 0.46 (1.53, 1.94)	1.73 ± 0.43 (1.52, 1.93)	0.34	0.44	0.42	.506	0.34
Posterior	1.39 ± 0.49 (1.13, 1.65)	1.35 ± 0.47 (1.12, 1.59)	1.57 ± 0.40 (1.38, 1.76)	1.68 ± 0.34 (1.52, 1.85)	0.64	0.02	0.99	.460	0.30
Alpha/Theta Ratio									
Frontal	2.89 ± 2.34 (1.64, 4.14)	2.87 ± 2.23 (1.76, 3.98)	2.26 ± 1.86 (1.39, 3.13)	2.19 ± 0.98 (1.72, 2.66)	0.69	0.22	0.92	.809	0.70
Central	3.02 ± 1.70 (2.12, 3.93)	3.12 ± 1.90 (2.17, 4.06)	2.57 ± 1.10 (2.05, 3.08)	2.92 ± 0.97 (2.45, 3.39)	0.26	0.45	0.65	.797	0.67
Posterior	4.39 ± 2.62 (2.99, 5.79)	4.15 ± 2.73 (2.79, 5.51)	3.40 ± 2.03 (2.45, 4.36)	2.96 ± 0.94 (2.50, 3.41)	0.24	0.07	0.66	.772	0.64
Peak Alpha Power (Hz)									
Frontal	9.84 ± 0.59 (9.53, 10.15)	9.94 ± 0.63 (9.62, 10.25)	9.89 ± 0.54 (9.58, 10.08)	9.73 ± 0.75 (9.37, 10.09)	0.92	0.51	0.42	.640	0.48
Central	9.95 ± 0.55 (9.65, 10.24)	9.98 ± 0.70 (9.64, 10.33)	9.93 ± 0.59 (9.66, 10.21)	10.07 ± 0.81 (9.68, 10.46)	0.56	0.94	0.63	.690	0.54
Posterior	9.98 ± 0.76 (9.57, 10.38)	10.23 ± 0.71 (9.88, 10.58)	9.99 ± 0.64 (9.69, 10.29)	10.04 ± 0.65 (9.73, 10.35)	0.28	0.49	0.38	.816	0.69

CHAPTER 8

DISSERTATION SUMMARY

Concussions are a large public health concern, and increasingly more attention and research is focused on concussion in hopes of better understanding factors to prevent, diagnosis, and manage injury.[85] Research has heavily focused on the clinical symptoms and deficits resulting from concussion. Symptom, balance, and cognitive deficits are typically resolved within 10 days of injury in collegiate populations following current clinical management of physical rest.[21] However, more active rehabilitation strategies are being advised to aid in the recovery process, which may be especially beneficial for individuals on prolonged recovery trajectories.[12] Researchers have begun using exercise interventions as therapeutic tools, with early results displaying positive findings.[8,14,234] Both the research on post-concussion exercise interventions and the clinical symptoms and deficits following concussion are limited by the same factor: a lack of thorough investigation into the physiological underpinnings driving dysfunction and subsequent recovery.

Previous research demonstrates exercise interventions to be safe,[57] reduce concussive symptoms,[6,8,14,234] and improve cognitive and mood outcomes[8] following concussion. Unfortunately, most of these studies do not thoroughly describe the feasibility and adherence to the prescribed training protocol. The increased heart rate, rate of perceived exertion, and increased workload (in watts) at training session termination provide evidence that ACTIVE training is progressively more difficult, as intended. Missed sessions were generally low and evenly distributed over the training period. This data, along with the high adherence to training intensity within each session, supports our hypothesis that ACTIVE training is feasible and

tolerable for healthy populations (Aim 3) and suggests no effect of burnout or overtraining associated with the protocol.

Concussions are known to result in acute physiological dysfunction, namely to cerebral metabolism,[89] cerebrovascular reactivity,[61] and cerebral blood flow.[61] Understanding the physiological influence of exercise interventions can provide a mechanistic rationale for the improvements brought about by these interventions and become a necessary starting point for the creation of more specific post-concussion exercise prescription guidelines designed to provide clinicians with clear indications for prescribing and monitoring injury rehabilitation. The ACTIVE training was able to significantly increase heart rate, percentage of predicted maximal heart rate, test duration, and ventilatory threshold outcomes relative to the control group, despite its brief training window. These improvements highlight the effectiveness of ACTIVE training in improving cardiopulmonary outcomes, supporting our hypothesis for Aim 2. The improved cardiopulmonary outcomes following ACTIVE training provide an important proof of concept that aerobic training may be clinically beneficial post-concussion as the intervention can influence physiological domains affected following injury as well as assist in the maintenance of physical conditioning throughout the recovery process.

Aerobic exercise can drive neural and clinical changes, which has important implications for better understanding clinical concussion deficits and the physiological factors driving clinical change. Electroencephalograms (EEGs) are relatively inexpensive, portable, and easily administered assessments in relation to other neuroimaging techniques (e.g. MRI), and their high temporal resolution may be particular harmonious to studying the neural underpinnings of clinical concussive deficits.[161] The ACTIVE training protocol significantly increased mean alpha power and the intervention group had higher mean theta, with significantly findings concentrated in the central ROI. These findings support our hypothesis that ACTIVE training would be effective in improving EEG outcomes (Aim 2) and the relationship between alpha and theta power and psychological and clinical cognitive outcomes can be explored in future studies. Most

EEG outcomes showed good to high reliability over time, with mean alpha power displaying the most reliable metrics. Electroencephalograms are currently used infrequently in concussion diagnosis and management, but their general stability, unaltered outcomes to exercise training, and high temporal resolution make them a candidate for future investigations into their utility as a diagnostic and management tools. However, more thorough investigations of specific EEG biomarkers and their psychometric properties, including their sensitivity and specificity, reliability over time, and reliable change indices, must be conducted before this tool can be used clinically.

Clinical assessments are very inexpensive, quickly administered, and relatively easy to interpret. They have been extensively vetted in the scientific literature, which renders them widely accessible and useful tools. All clinical outcomes assessed throughout this study were stable in response to ACTIVE training. The lack of mean differences outside reliable change disagrees with our hypothesis for Aim 1, but speaks to the high clinical utility of the current clinical concussion battery as our data suggest these assessments are unaffected by repeated exercise administration. Thus, we believe any clinically significant improvements seen in these assessments in injured populations will represent healing, negating the need for adjusted scores or other metrics to enhance interpretation of these tests in patients receiving exercise therapy.

Overall, the ACTIVE training intervention is feasible and is effective at improving cardiopulmonary and EEG outcomes program in healthy, collegiate populations. Clinical concussion assessments were stable in response to ACTIVE training, a positive finding that suggests clinicians can interpret clinical assessments in concussed populations as currently recommended. This study has high clinical importance in translating findings to future studies investigating concussed participants. Exercise alone does not influence clinical concussion outcomes, negating the necessity of adjusted scores to interpret results and reducing the chance of prematurely returning athletes to play. The ACTIVE training protocol improved cardiopulmonary outcomes, which may serve as a theoretical basis for targeting physiological

domains affected post-concussion and help athletes maintain physical fitness during the recovery period. Improvements in EEG outcomes correlated to psychological outcomes, indicating the ACTIVE training may not only benefit physiological health, but may also improve anxiety or depression scores. Future studies should investigate ACTIVE training in acutely concussed participants, as well as healthy and injured youth athletes, to confirm its utility and appropriateness in these populations as they may respond differently than the healthy participants tested here. This will be dedicated area of research that will be developed in my early career, and the data observed in my dissertation will provide the scientific rational and physiological underpinning for intervention development moving forward.

APPENDIX A

DATA COLLECTION FORMS

1. Screening Forms
    a. Physical Activity Readiness Questionnaire
    b. Medical History Questionnaire
2. Demographics Form
3. Pre-Test Guidelines for Maximal Exercise Tests
4. Standardized Assessment of Concussion
5. Balance Error Scoring System
6. Vestibular/Ocular Motor Screening
7. Graded Symptom Checklist
8. Maximal Exercise Test Data Collection Form
9. Cardiovascular Assessment Form

Physical Activity Readiness Questionnaire (PAR-Q) and You

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly:

Yes	No		
□	□	**1.**	Has your doctor ever said that you have a heart condition and that you should not do physical activity recommended by a doctor?
□	□	**2.**	Do you feel pain in your chest when you do physical activity?
□	□	**3.**	In the past month, have you had chest pain when you were not doing physical activity?
□	□	**4.**	Do you lose your balance because of dizziness or do you ever lose consciousness?
□	□	**5.**	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
□	□	**6.**	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
□	□	**7.**	Do you know of any other reason why you should not do physical activity?

I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction.

Name _____

Signature _____ Date _____

Signature of Parent _____ Witness _____

or Guardian (for participants under the age of majority)

Department of Exercise and Sport Science
Medical History

Subject ID:_____

Age:_____

YES NO

Patient History

1. How would you describe your general health at present?
   Excellent_____ Good_____ Fair_____ Poor_____
2. Do you have any health problems at the present time? _____ _____
3. If yes, please describe:_____
4. Have you ever been told you have heart trouble? _____ _____
5. If yes, please describe:_____
6. Do you ever get pain in your chest? _____ _____
7. Do you ever feel light-headed or have you ever fainted? _____ _____
8. If yes, please describe:_____
9. Have you ever been told that your blood pressure has been elevated? _____ _____
10. If yes, please describe:_____
11. Have you ever had difficulty breathing either at rest or with exertion? _____ _____
12. If yes, please describe:_____
13. Are you now, or have you been in the past 5 years, under a doctor's care for any reason? _____ _____
14. If yes for what reason?_____
15. Have you been in the hospital in the past 5 years? _____ _____
16. If yes, for what reason?_____
17. Have you ever experienced an epileptic seizure or been informed that you have epilepsy? _____ _____
18. Have you ever been treated for infectious mononucleosis, hepatitis, pneumonia, or another infectious disease during the past year? _____ _____
19. If yes, name the disease:_____
20. Have you ever been treated for or told you might have diabetes? _____ _____
21. Have you ever been treated for or told you might or low blood sugar? _____ _____
22. Do you have any known allergies to drugs? _____ _____
23. If so, what?_____
24. Have you ever been "knocked-out" or experienced a concussion? _____ _____
25. If yes, have you been "knocked-out" more than once? _____ _____
26. Have you ever experienced heat stroke or heat exhaustion? _____ _____
27. If yes, when?_____

28. Have you ever had any additional illnesses or operations? (Other than childhood diseases) _____ _____

29. If yes, please indicate specific illness or operations:_____

_____

30. Are you now taking any pills or medications? _____ _____

31. If yes, please list:_____

_____

32. Have you had any recent (within 1 year) difficulties with your:

a. Feet _____ _____
b. Legs _____ _____
c. Back _____ _____

Family History

33. Has anyone in your family (grandparent, father, mother, and/or sibling) experienced any of the following?

a. Sudden death _____ _____
b. Cardiac disease _____ _____
c. Marfan's syndrome _____ _____

Mental History

34. Have you ever experienced depression? _____ _____

35. If yes, did you seek the advice of a doctor? _____ _____

36. Have you ever been told you have or has a doctor diagnosed you with panic disorder, obsessive-compulsive disorder, clinical depression, bipolar disorder, or any other psychological disease? _____ _____

37. If yes, please list condition and if you are currently taking any medication.

Condition Medication

_____

_____

_____

Bone and Joint History

34. Have you ever been treated for Osgood-Schlatter's disease? _____ _____

35. Have you ever had any injury to your neck involving nerves or vertebrae? _____ _____

36. Have you ever had a shoulder dislocation, separation, or other injury of the shoulder that incapacitated you for a week or longer? _____ _____

37. Have you ever been advised to or have you had surgery to correct a shoulder condition? _____ _____

38. Have you ever experienced any injury to your arms, elbows, or wrists?_____ _____

39. If yes, indicate location and type of injury:_____

_____

40. Do you experience pain in your back? _____ _____

41. Have you ever had an injury to your back? _____ _____

42. If yes, did you seek the advice of a doctor? _____ _____

43. Have you ever been told that you injured the ligaments or cartilage of either knee joint? _____ _____

44. Do you think you have a trick knee? _____ _____

45. Do you have a pin, screw, or plate somewhere in your body as the result of bone or joint surgery that presently limits your physical capacity? _____ ____

46. If yes, indicate where:_____

_____

47. Have you ever had a bone graft or spinal fusion? _____ _____

Activity History

48. During your early childhood (to age 12) would you say you were:
    Very active ____ Quite active____ Moderately active____ Seldom active____
49. During your adolescent years (age 13-18) would you say you were:
    Very active ____ Quite active____ Moderately active____ Seldom active____
50. Did you participate in:
    a. Intramural school sports? _____ _____
    b. Community sponsored sports? _____ _____
    c. Varsity school sports? _____ _____
    d. Active family recreation? _____ _____
51. Since leaving high school, how active have you been?
    Very active ____ Quite active____ Active____ Inactive____
52. Do you participate in any vigorous activity at present? _____ _____
53. If yes, please list:

Activity	Frequency	Duration	Intensity

54. How would you describe your present state of fitness?
Excellent_____ Good_____ Fair_____ Poor_____
55. Please list the type(s) of work you have been doing for the previous ten years:

Year	Work	Indoor/Outdoor	Location (city/state)

56. Whom shall we notify in case of emergency?
    Name:_____
    Phone: (Home)_____ (Work)_____
    Address:_____
57. Name and address of personal physician:_____

_____

_____

All of the above questions have been answered completely and truthfully to the best of my knowledge.

Signature:_____ Date:_____

Subject ID: _____ email: _____

Date of Birth: _____ Handedness: Right Left Sex: Male Female

Date of Concussion: _____ Sport: _____ Position: _____

Current Grade: _____ Current GPA: _____ EEG Cap Size*: _____

If you are recently concussed, did you sustain any other injuries at the time of your concussion?	□ **Yes**	□ **No**
⇨ **If yes, please specify:**		
Was your concussion the result of a sports-related activity?	□ **Yes**	□ **No**
Are you symptoms gradually worsening over time?	□ **Yes**	□ **No**
⇨ **If yes, please explain:**		
Did you lose consciousness during your concussion?	□ **Yes**	□ **No**
⇨ **If yes, please state for how long:**		
Did you lose your memory immediately ***before*** the concussion?	□ **Yes**	□ **No**
⇨ **If yes, please state for how long:**		
Did you lose your memory immediately ***after*** the concussion?	□ **Yes**	□ **No**
⇨ **If yes, please state for how long:**		
Have you previously sustained a concussion?	□ **Yes**	□ **No**
⇨ **If yes, please list number and approximate dates:**		
Are you currently on any prescription medicine?	□ **Yes**	□ **No**
⇨ **If yes, please specify:**		
Are you currently on any over the counter medicine?	□ **Yes**	□ **No**
⇨ **If yes, please specify:**		
Do you currently use any recreational drugs?	□ **Yes**	□ **No**

Have ***you*** ever been diagnosed with any of the following?

- □ **ADHD**
- □ **ADD**
- □ **Learning Disability**
- □ **Seizures**
- □ **Psychiatric Condition**
- □ **Depression**
- □ **Anxiety**
- □ **Migraines**

If yes, please specify date of diagnosis:

Has anyone in your ***immediate family*** been diagnosed the following?

- □ **ADHD**
- □ **ADD**
- □ **Learning Disability**
- □ **Seizures**
- □ **Psychiatric Conditions**
- □ **Depression**
- □ **Anxiety**
- □ **Migraines**

If yes, please specify relationship to you:

On average, how fit are you relative to your peers? (please circle)	Much less fit	Somewhat less fit	Just as fit	Somewhat more fit	Much more fit

UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL
Claudio Battaglini, Ph.D. FACSM.
Department of Exercise and Sport Sciences
105 Fetzer Hall, CB # 8700
(919) 843-6045 / Email: claudio@email.unc.edu

Pre-Test Guidelines

1. Avoid eating 2 hours prior to testing.
2. Void completely before testing.
3. Maintain proper hydration prior to testing.
4. Please wear appropriate clothing/shoes for testing (running shorts/shirt/shoes)
5. No exercise 12 hours prior to testing.
6. No alcohol consumption 48 hours prior to testing.
7. No diuretic medications 7 days prior to testing.

Source: Advanced Fitness Assessment and Exercise Prescription – Third Edition – Vivian H. Heyward

Subject ID: _____ Date: _____ Session: 1 2

Standardized Assessment of Concussion

INTRODUCTION:

I am going to ask you some questions.
Please listen carefully and give your best effort.

ORIENTATION

What Month is it?	0	1
What's the Date today?	0	1
What's the Day of Week?	0	1
What Year is it?	0	1
What Time is it right now? (within 1 hr.)	0	1

Award 1 point for each correct answer.

ORIENTATION TOTAL SCORE ➡ ☐

IMMEDIATE MEMORY

I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order.

LIST	TRIAL 1	TRIAL 2	TRIAL 3
ELBOW	0 1	0 1	0 1
APPLE	0 1	0 1	0 1
CARPET	0 1	0 1	0 1
SADDLE	0 1	0 1	0 1
BUBBLE	0 1	0 1	0 1
TOTAL			

Trials 2 & 3: **I am going to repeat that list again. Repeat back as many words as you can remember in any order, even if you said the word before.**

Complete all 3 trials regardless of score on trial 1 & 2. 1 pt. for each correct response. Total score equals sum across all 3 trials.

Do not inform the subject that delayed recall will be tested.

IMMEDIATE MEMORY TOTAL SCORE ➡ ☐

CONCENTRATION

***Digits Backward*: I am going to read you a string of numbers and when I am done, you repeat them back to me backwards, in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7.**

If correct, go to next string length. If incorrect, read trial 2. 1 pt. possible for each string length. Stop after incorrect on both trials.

4-9-3	**6-2-9**	0 1
3-8-1-4	**3-2-7-9**	0 1
6-2-9-7-1	**1-5-2-8-6**	0 1
7-1-8-4-6-2	**5-3-9-1-4-8**	0 1

***Months in Reverse Order*: Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November...Go ahead.** 1 pt. for entire sequence correct.

Dec-Nov-Oct-Sept-Aug-Jul-Jun-May-Apr-Mar-Feb-Jan 0 1

CONCENTRATION TOTAL SCORE ➡ ☐

DELAYED RECALL

Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order. Circle each word correctly recalled. Total score equals number of words recalled.

ELBOW APPLE CARPET SADDLE BUBBLE

DELAYED RECALL TOTAL SCORE ➡ ☐

Subject ID: _____ Date: _____ Session: 1 2

Balance Error Scoring System

Balance Error Scoring System- Types of Errors
1. Hands lifted off iliac crest **2. Opening eyes** **3. Step, stumble, fall** **4. Moving hip >30 degrees abduction** **5. Lifting forefoot or heel** **6. Remaining out test position >5 seconds**
The BESS is calculated by adding one error point for each error during the 6 20-second test.

Which foot was tested: LEFT RIGHT
(ie. Which is the non-dominant foot?)

SCORE CARD	Firm Surface	Foam Surface
Double Leg Stance (feet together)		
Single Leg Stance (non-dominant foot)		
Tandem Stance (non-dom foot in back)		
Total Scores:		
BESS TOTAL:		

Subject ID: _____ Date: _____ Session: 1 2

Vestibular/Ocular Motor Screening

	Headache	Dizziness	Nausea	Fogginess	Comments
Baseline					
Smooth Pursuits					
Saccades (Horizontal)					
Saccades (Vertical)					
Convergence					T1: _____ cm T2: _____ cm T3: _____ cm
VOR Horizontal					
VOR Vertical					
Visual Motion Sensitivity					

Subject ID: _____ Date:_____ Session: 1 2

Graded Symptom Checklist

Symptom	Prior to ACTIVE Session	Immediately following ACTIVE	15mins following ACTIVE
Blurred Vision			
Dizziness			
Drowsiness			
Excess Sleep			
Easily Distracted			
Fatigue			
Feel “in a fog”			
Feel “slowed down”			
Headache			
Inappropriate emotions			
Irritability			
Loss of consciousness			
Loss of orientation			
Memory problems			
Nausea			
Nervousness			
Personality changes			
Poor balance			
Poor concentration			
Ringing in ears			
Sadness			
Seeing stars			
Sensitivity to light			
Sensitivity to noise			
Sleep disturbance			
Vacant stare			
Vomiting			
Rate as “0” if symptom not present. If present, rate symptom from mild (“1”) to severe (“6”).			

Subject ID:_____ Date:_____ Session: 1 2

Maximal Exercise Test	HR	RPE
0:00- Begin pedaling at 50 W		
1:00- Maintain 50 W		
2:00- Increase to 100 W		
3:00- Maintain 100 W		
4:00- Increase to 150 W		
5:00- Maintain 150 W		
6:00- Increase to 180 W		
7:00- Maintain 180 W		
8:00- Increase to 210 W		
9:00- Maintain 210 W		
10:00- Increase to 240 W		
11:00- Increase to 270 W		
12:00- Increase to 300 W		
13:00- Increase to 330 W		
14:00- Increase to 360 W		
15:00- Increase to 390 W		
16:00- Increase to 420 W		
17:00- Increase to 450 W		
18:00- Increase to 480 W		
19:00- Increase to 510 W		
20:00- Increase to 540 W		
Termination- volition or symptom exacerbation		

Time at protocol termination_____

HR at protocol termination: _____

RPE at protocol termination: _____

Cardiovascular Assessment Form

Subject ID: _____

Time of testing: _____

Age: _____yrs

Birthday:_____

Height: _____ cm

Weight: _____kg

Mask Size: _____

Seat Height:_____ in

Pre-Exercise Measures

RHR:_____

RBP:_____

VO_2peak:

_____(ml/kg/min)

_____(L/min)

Lactate:_____(mmol/L)

Post-Exercise Measures

RHR:_____

RBP:_____

VO_2peak:

_____(ml/kg/min)

_____(L/min)

Lactate:_____(mmol/L)

HRR: _____

HRR= ((220-Age) – Resting HR) x % + Resting HR

REFERENCES

1. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil.* 2006;21(5):375-378.

2. Silverberg ND, Iverson GL. Is rest after concussion" the best medicine?": recommendations for activity resumption following concussion in athletes, civilians, and military service members. *The Journal of head trauma rehabilitation.* 2013;28(4):250-259.

3. Yi J, Padalino DJ, Chin LS, Montenegro P, Cantu RC. Chronic traumatic encephalopathy. *Current sports medicine reports.* 2013;12(1):28-32.

4. Blume HK, Lucas S, Bell KR. Subacute concussion-related symptoms in youth. *Physical medicine and rehabilitation clinics of North America.* 2011;22(4):665-681.

5. Leddy JJ, Cox JL, Baker JG, et al. Exercise treatment for postconcussion syndrome: a pilot study of changes in functional magnetic resonance imaging activation, physiology, and symptoms. *The Journal of head trauma rehabilitation.* 2013;28(4):241-249.

6. Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine.* 2010;20(1):21-27.

7. Gagnon I, Galli C, Friedman D, Grilli L, Iverson GL. Active rehabilitation for children who are slow to recover following sport-related concussion. *Brain injury.* 2009;23(12):956-964.

8. Gagnon I, Grilli L, Friedman D, Iverson GL. A pilot study of active rehabilitation for adolscents who are slow to recover from sports-related concussion. *Scandinavian Journal of Medicine & Science in Sports.* 2015.

9. Aubry M, Cantu R, Dvorak J, et al. Summary and agreement statement of the first International Conference on Concussion in Sport, Vienna 2001. *British journal of sports medicine.* 2002;36(1):6-7.

10. Bazarian JJ, Atabaki S. Predicting postconcussion syndrome after minor traumatic brain injury. *Academic Emergency Medicine.* 2001;8(8):788-795.

11. Ryan LM, Warden DL. Post concussion syndrome. *International review of psychiatry (Abingdon, England).* 2003;15(4):310-316.

12. Silverberg ND, Iverson GL. Is rest after concussion "the best medicine?": recommendations for activity resumption following concussion in athletes, civilians, and military service members. *J Head Trauma Rehabil.* 2013;28(4):250-259.

13. Elbin RJ, Schatz P, Lowder HB, Kontos AP. An empirical review of treatment and rehabilitation approaches used in the acute, sub-acute, and chronic phases of recovery following sports-related concussion. *Current treatment options in neurology.* 2014;16(11):320.

14. Baker JG, Freitas MS, Leddy JJ, Kozlowski KF, Willer BS. Return to full functioning after graded exercise assessment and progressive exercise treatment of postconcussion syndrome. *Rehabilitation research and practice.* 2012;2012:705309.

15. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA.* 2003;290(19):2549-2555.

16. Bey T, Ostick B. Second impact syndrome. *Western Journal of Emergency Medicine.* 2009;10(1):6.

17. Sefton JM. *An examination of factors that influence knowledge of and reporting of head injuries in college football*, Central Connecticut State University; 2003.

18. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nature reviews neuroscience.* 2008;9(1):58-65.

19. Jones AM, Carter H. The effect of endurance training on parameters of aerobic fitness. *Sports medicine.* 2000;29(6):373-386.

20. Slobounov S, Gay M, Johnson B, Zhang K. Concussion in athletics: ongoing clinical and brain imaging research controversies. *Brain imaging and behavior.* 2012;6(2):224-243.

21. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *British journal of sports medicine.* 2013;47(5):250-258.

22. Fox ZG, Mihalik JP, Blackburn JT, Battaglini CL, Guskiewicz KM. Return of postural control to baseline after anaerobic and aerobic exercise protocols. *J Athl Train.* 2008;43(5):456-463.

23. Covassin T, Weiss L, Powell J, Womack C. Effects of a maximal exercise test on neurocognitive function. *Br J Sports Med.* 2007;41(6):370-374; discussion 374.

24. Topp R, Mikesky A, Dayhoff NE, Holt W. Effect of resistance training on strength, postural control, and gait velocity among older adults. *Clinical Nursing Research.* 1996;5(4):407-427.

25. Alla S, Sullivan SJ, McCrory P, Schneiders AG, Handcock P. Does exercise evoke neurological symptoms in healthy subjects? *Journal of science and medicine in sport / Sports Medicine Australia.* 2010;13(1):24-26.

26. Gaetz MB, Iverson GL. Sex differences in self-reported symptoms after aerobic exercise in non-injured athletes: implications for concussion management programmes. *Br J Sports Med.* 2009;43(7):508-513.

27. Lee H, Sullivan SJ, Schneiders AG. Does a standardised exercise protocol incorporating a cognitive task provoke postconcussion-like symptoms in healthy individuals? *Journal of science and medicine in sport / Sports Medicine Australia.* 2015;18(3):245-249.

28. Wilkins JC, Valovich McLeod TC, Perrin DH, Gansneder BM. Performance on the Balance Error Scoring System Decreases After Fatigue. *J Athl Train.* 2004;39(2):156-161.

29. Deslandes A, Moraes H, Alves H, et al. Effect of aerobic training on EEG alpha asymmetry and depressive symptoms in the elderly: a 1-year follow-up study. *Brazilian Journal of Medical and Biological Research.* 2010;43(6):585-592.

30. Bongers BC, De Vries SI, Helders PJ, Takken T. The steep ramp test in healthy children and adolescents: reliability and validity. *Med Sci Sports Exerc.* 2013;45(2):366-371.

31. Lovell MR, Iverson GL, Collins MW, et al. Measurement of symptoms following sports-related concussion: reliability and normative data for the post-concussion scale. *Applied neuropsychology.* 2006;13(3):166-174.

32. Register-Mihalik JK, Guskiewicz KM, Mihalik JP, Schmidt JD, Kerr ZY, McCrea MA. Reliable change, sensitivity, and specificity of a multidimensional concussion assessment battery: implications for caution in clinical practice. *J Head Trauma Rehabil.* 2013;28(4):274-283.

33. Littleton AC, Register-Mihalik JK, Guskiewicz KM. Test-Retest Reliability of a Computerized Concussion Test CNS Vital Signs. *Sports Health: A Multidisciplinary Approach.* 2015:1941738115586997.

34. Teel EF, Register-Mihalik JK, Blackburn JT, Guskiewicz KM. Balance and cognitive performance during a dual-task: preliminary implications for use in concussion assessment. *Journal of Science and Medicine in Sport.* 2013;16(3):190-194.

35. Mihalik JP, Lengas E, Register-Mihalik JK, Oyama S, Begalle RL, Guskiewicz KM. The effects of sleep quality and sleep quantity on concussion baseline assessment. *Clinical Journal of Sport Medicine.* 2013;23(5):343-348.

36. Register-Mihalik JK, Kontos DL, Guskiewicz KM, Mihalik JP, Conder R, Shields EW. Age-related differences and reliability on computerized and paper-and-pencil neurocognitive assessment batteries. *Journal of athletic training.* 2012;47(3):297.

37. McCrea M. Standardized mental status testing on the sideline after sport-related concussion. *Journal of athletic training.* 2001;36(3):274.

38. McLeod TCV, Barr WB, McCrea M, Guskiewicz KM. Psychometric and measurement properties of concussion assessment tools in youth sports. *Journal of athletic training.* 2006;41(4):399.

39. Barr WB, McCREA M. Sensitivity and specificity of standardized neurocognitive testing immediately following sports concussion. *Journal of the International Neuropsychological Society.* 2001;7(06):693-702.

40. Riemann BL, Guskiewicz KM. Effects of mild head injury on postural stability as measured through clinical balance testing. *Journal of athletic training.* 2000;35(1):19.

41. Riemann BL, Guskiewicz KM, Shields EW. Relationship between clinical and forceplate measures of postural stability. *Journal of Sport Rehabilitation.* 1999;8:71-82.

42. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *Jama.* 2003;290(19):2556-2563.

43. Mucha A, Collins MW, Elbin R, et al. A Brief Vestibular/Ocular Motor Screening (VOMS) Assessment to Evaluate Concussions Preliminary Findings. *The American journal of sports medicine.* 2014:0363546514543775.

44. Bailey SP, Hall EE, Folger SE, Miller PC. Changes in EEG during graded exercise on a recumbent cycle ergometer. *Journal of sports science & medicine.* 2008;7(4):505.

45. Gay M, Ray W, Johnson B, Teel E, Geronimo A, Slobounov S. Feasibility of eeg measures in conjunction with light exercise for return-to-play evaluation after sports-related concussion. *Developmental neuropsychology.* 2015;40(4):248-253.

46. Wenger HA, Bell GJ. The interactions of intensity, frequency and duration of exercise training in altering cardiorespiratory fitness. *Sports medicine.* 1986;3(5):346-356.

47. Hickson R, Hagberg J, Ehsani A, Holloszy J. Time course of the adaptive responses of aerobic power and heart rate to training. *Medicine and Science in Sports and Exercise.* 1980;13(1):17-20.

48. Gaetz M, Bernstein DM. The current status of electrophysiologic procedures for the assessment of mild traumatic brain injury. *The Journal of head trauma rehabilitation.* 2001;16(4):386-405.

49. Cannon RL, Baldwin DR, Shaw TL, et al. Reliability of quantitative EEG (qEEG) measures and LORETA current source density at 30 days. *Neuroscience letters.* 2012;518(1):27-31.

50. Broglio SP, Pontifex MB, O'Connor P, Hillman CH. The persistent effects of concussion on neuroelectric indices of attention. *J Neurotrauma.* 2009;26(9):1463-1470.

51. Nuwer MR, Hovda DA, Schrader LM, Vespa PM. Routine and quantitative EEG in mild traumatic brain injury. *Clin Neurophysiol.* 2005;116(9):2001-2025.

52. Cooper JA, Watras AC, O'Brien MJ, et al. Assessing validity and reliability of resting metabolic rate in six gas analysis systems. *Journal of the American Dietetic Association.* 2009;109(1):128-132.

53. Crouter SE, Antczak A, Hudak JR, DellaValle DM, Haas JD. Accuracy and reliability of the ParvoMedics TrueOne 2400 and MedGraphics VO2000 metabolic systems. *European journal of applied physiology.* 2006;98(2):139-151.

54. Friedman JM. Post-traumatic vertigo. *Medicine and Health Rhode Island.* 2004;87(10):296.

55. Ingriselli JM, Register-Mihalik JK, Schmidt JD, Mihalik JP, Goerger BM, Guskiewicz KM. Outcomes, utility, and feasibility of single task and dual task intervention programs: preliminary implications for post-concussion rehabilitation. *Journal of Science and Medicine in Sport.* 2014;17(6):580-585.

56. Goodman J, Thomas S, Burr JF. Cardiovascular risks of physical activity in apparently healthy individuals.

57. Cordingley D, Girardin R, Reimer K, et al. Graded aerobic treadmill testing in pediatric sports-related concussion: safety, clinical use, and patient outcomes. *Journal of Neurosurgery: Pediatrics.* 2016;18(6):693-702.

58. Maerlender A, Rieman W, Lichtenstein J, Condiracci C. Programmed physical exertion in recovery from sports-related concussion: a randomized pilot study. *Developmental neuropsychology.* 2015;40(5):273-278.

59. Pfeiffer KA, Pivarnik JM, Womack CJ, Reeves MJ, Malina RM. Reliability and validity of the Borg and OMNI rating of perceived exertion scales in adolescent girls. *Medicine and science in sports and exercise.* 2002;34(12):2057-2061.

60. Borg E, Kaijser L. A comparison between three rating scales for perceived exertion and two different work tests. *Scandinavian journal of medicine & science in sports.* 2006;16(1):57-69.

61. Tan CO, Meehan WP, 3rd, Iverson GL, Taylor JA. Cerebrovascular regulation, exercise, and mild traumatic brain injury. *Neurology.* 2014;83(18):1665-1672.

62. Ellis MJ, Leddy JJ, Willer B. Physiological, vestibulo-ocular and cervicogenic post-concussion disorders: an evidence-based classification system with directions for treatment. *Brain injury.* 2015;29(2):238-248.

63. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *Journal of athletic training.* 2001;36(3):228.

64. Broglio SP, Cantu RC, Gioia GA, et al. National Athletic Trainers' Association position statement: management of sport concussion. *Journal of athletic training.* 2014;49(2):245.

65. Leddy JJ, Kozlowski K, Fung M, Pendergast DR, Willer B. Regulatory and autoregulatory physiological dysfunction as a primary characteristic of post concussion syndrome: implications for treatment. *NeuroRehabilitation.* 2007;22(3):199-205.

66. Kurowski BG, Hugentobler J, Quatman-Yates C, et al. Aerobic Exercise for Adolescents With Prolonged Symptoms After Mild Traumatic Brain Injury: An Exploratory Randomized Clinical Trial. *The Journal of head trauma rehabilitation.* 2016.

67. Grabowski P, Wilson J, Walker A, Enz D, Wang S. Multimodal impairment-based physical therapy for the treatment of patients with post-concussion syndrome: A retrospective analysis on safety and feasibility. *Physical Therapy in Sport.* 2016.

68. Gagnon I, Grilli L, Friedman D, Iverson GL. A pilot study of active rehabilitation for adolescents who are slow to recover from sport-related concussion. *Scandinavian journal of medicine & science in sports.* 2015.

69. Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *British journal of sports medicine.* 2013;47(5):304-307.

70. McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz K. Unreported concussion in high school football players: implications for prevention. *Clinical Journal of Sport Medicine.* 2004;14(1):13-17.

71. Gagnon I, Galli C, Friedman D, Grilli L, Iverson GL. Active rehabilitation for children who are slow to recover following sport-related concussion. *Brain injury.* 2009;23(12):956-964.

72. Dematteo C, Volterman KA, Breithaupt PG, Claridge EA, Adamich J, Timmons BW. Exertion Testing in Youth with Mild Traumatic Brain Injury/Concussion. *Med Sci Sports Exerc.* 2015;47(11):2283-2290.

73. Chen X, Tao L, Cn Chen A. Electroencephalogram and evoked potential parameters examined in Chinese mild head injury patients for forensic medicine. *Neuroscience Bulletin.* 2006;22(3):165.

74. Gosselin N, Thériault M, Leclerc S, Montplaisir J, Lassonde M. Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. *Neurosurgery.* 2006;58(6):1151-1161.

75. Korn A, Golan H, Melamed I, Pascual-Marqui R, Friedman A. Focal cortical dysfunction and blood–brain barrier disruption in patients with Postconcussion syndrome. *Journal of Clinical Neurophysiology.* 2005;22(1):1-9.

76. Arciniegas DB. Clinical electrophysiologic assessments and mild traumatic brain injury: state-of-the-science and implications for clinical practice. *Int J Psychophysiol.* 2011;82(1):41-52.

77. Collins MW, Grindel SH, Lovell MR, et al. Relationship between concussion and neuropsychological performance in college football players. *Jama.* 1999;282(10):964-970.

78. Iverson GL, Gaetz M, Lovell MR, Collins MW. Relation between subjective fogginess and neuropsychological testing following concussion. *Journal of the International Neuropsychological Society.* 2004;10(06):904-906.

79. Grady MF. Concussion in the adolescent athlete. *Current problems in pediatric and adolescent health care.* 2010;40(7):154-169.

80. Schneider KJ, Meeuwisse WH, Nettel-Aguirre A, et al. Cervicovestibular rehabilitation in sport-related concussion: a randomised controlled trial. *British journal of sports medicine.* 2014:bjsports-2013-093267.

81. Alsalaheen BA, Mucha A, Morris LO, et al. Vestibular rehabilitation for dizziness and balance disorders after concussion. *Journal of Neurologic Physical Therapy.* 2010;34(2):87-93.

82. Thiagarajan P, Ciuffreda KJ. Effect of oculomotor rehabilitation on accommodative responsivity in mild traumatic brain injury. *Journal of rehabilitation research and development.* 2014;51(2):175-191.

83. Thiagarajan P, Ciuffreda KJ. Versional eye tracking in mild traumatic brain injury (mTBI): effects of oculomotor training (OMT). *Brain injury.* 2014;28(7):930-943.

84. Thiagarajan P, Ciuffreda KJ. Effect of oculomotor rehabilitation on vergence responsivity in mild traumatic brain injury. *Journal of rehabilitation research and development.* 2013;50(9):1223-1240.

85. Wiebe DJ, Comstock RD, Nance ML. Concussion research: a public health priority. *Injury prevention.* 2011;17(1):69-70.

86. Barkhoudarian G, Hovda DA, Giza CC. The molecular pathophysiology of concussive brain injury. *Clinics in sports medicine.* 2011;30(1):33-48.

87. Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. *J Athl Train.* 2001;36(3):228-235.

88. Lovell MA. The neurophysiology and assessment of sports-related head injuries. *Neurologic Clinics.* 2009;26(1):45-62.

89. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery.* 2014;75(0 4):S24.

90. Gall B, Parkhouse WS, Goodman D. Exercise following a sport induced concussion. *Br J Sports Med.* 2004;38(6):773-777.

91. King M, Lichtman S, Seliger G, Ehert F, Steinberg J. Heart-rate variability in chronic traumatic brain injury. *Brain injury.* 1997;11(6):445-453.

92. La Fountaine MF, Heffernan KS, Gossett JD, Bauman WA, De Meersman RE. Transient suppression of heart rate complexity in concussed athletes. *Autonomic neuroscience : basic & clinical.* 2009;148(1-2):101-103.

93. Abaji JP, Curnier D, Moore RD, Ellemberg D. Persisting Effects of Concussion on Heart Rate Variability during Physical Exertion. *J Neurotrauma.* 2015.

94. Gall B, Parkhouse W, Goodman D. Heart rate variability of recently concussed athletes at rest and exercise. *Med Sci Sports Exerc.* 2004;36(8):1269-1274.

95. La Fountaine MF, Gossett JD, De Meersman RE, Bauman WA. Increased QT interval variability in 3 recently concussed athletes: an exploratory observation. *J Athl Train.* 2011;46(3):230-233.

96. Goldstein B, Toweill D, Lai S, Sonnenthal K, Kimberly B. Uncoupling of the autonomic and cardiovascular systems in acute brain injury. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology.* 1998;275(4):R1287-R1292.

97. Gardner AJ, Tan CO, Ainslie PN, et al. Cerebrovascular reactivity assessed by transcranial Doppler ultrasound in sport-related concussion: a systematic review. *Br J Sports Med.* 2015;49(16):1050-1055.

98. Len TK, Neary JP, Asmundson G, Goodman DG, Bjornson B, Bhambhani YN. Cerebrovascular reactivity impairment after sport-induced concussion. *Med Sci Sports Exerc.* 2011;43(12):2241-2248.

99. Clausen M, Pendergast DR, Willer B, Leddy J. Cerebral Blood Flow During Treadmill Exercise Is a Marker of Physiological Postconcussion Syndrome in Female Athletes. *J Head Trauma Rehabil.* 2015.

100. McCrory P, Meeuwisse W, Johnston K, et al. Consensus statement on Concussion in Sport–the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *South African Journal of sports medicine.* 2009;21(2).

101. Collins MW, Kontos AP, Reynolds E, Murawski CD, Fu FH. A comprehensive, targeted approach to the clinical care of athletes following sport-related concussion. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2014;22(2):235-246.

102. Moser RS, Glatts C, Schatz P. Efficacy of immediate and delayed cognitive and physical rest for treatment of sports-related concussion. *The Journal of pediatrics.* 2012;161(5):922-926.

103. Moser RS, Schatz P, Glenn M, Kollias KE, Iverson GL. Examining prescribed rest as treatment for adolescents who are slow to recover from concussion. *Brain injury.* 2015;29(1):58-63.

104. Thomas DG, Apps JN, Hoffmann RG, McCrea M, Hammeke T. Benefits of strict rest after acute concussion: a randomized controlled trial. *Pediatrics.* 2015;135(2):213-223.

105. Buckley TA, Munkasy BA, Clouse BP. Acute Cognitive and Physical Rest May Not Improve Concussion Recovery Time. *J Head Trauma Rehabil.* 2015.

106. Majerske CW, Mihalik JP, Ren D, et al. Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. *J Athl Train.* 2008;43(3):265-274.

107. Gibson S, Nigrovic LE, O'Brien M, Meehan WP, 3rd. The effect of recommending cognitive rest on recovery from sport-related concussion. *Brain injury.* 2013;27(7-8):839-842.

108. Brown NJ, Mannix RC, O'Brien MJ, Gostine D, Collins MW, Meehan WP, 3rd. Effect of cognitive activity level on duration of post-concussion symptoms. *Pediatrics.* 2014;133(2):e299-304.

109. Craton N, Leslie O. Is rest the best intervention for concussion? Lessons learned from the whiplash model. *Current sports medicine reports.* 2014;13(4):201-204.

110. Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports Med.* 2013;47(5):304-307.

111. Kramer AF, Erickson KI, Colcombe SJ. Exercise, cognition, and the aging brain. *Journal of Applied Physiology.* 2006;101(4):1237-1242.

112. Eggermont L, Swaab D, Luiten P, Scherder E. Exercise, cognition and Alzheimer's disease: more is not necessarily better. *Neuroscience & biobehavioral reviews.* 2006;30(4):562-575.

113. Verschueren SM, Roelants M, Delecluse C, Swinnen S, Vanderschueren D, Boonen S. Effect of 6‐Month Whole Body Vibration Training on Hip Density, Muscle Strength, and Postural Control in Postmenopausal Women: A Randomized Controlled Pilot Study. *Journal of bone and mineral research.* 2004;19(3):352-359.

114. Judge J, Underwood M, Gennosa T. Exercise to improve gait velocity in older persons. *Archives of physical medicine and rehabilitation.* 1993;74(4):400-406.

115. Broglio SP, Puetz TW. The effect of sport concussion on neurocognitive function, self-report symptoms and postural control. *Sports Medicine.* 2008;38(1):53-67.

116. Grool AM, Aglipay M, Momoli F, et al. Association Between Early Participation in Physical Activity Following Acute Concussion and Persistent Postconcussive Symptoms in Children and Adolescents. *Jama.* 2016;316(23):2504-2514.

117. Kontos AP, Elbin R, Schatz P, et al. A revised factor structure for the post-concussion symptom scale baseline and postconcussion factors. *The American journal of sports medicine.* 2012:0363546512455400.

118. Hunt T, Asplund C. Concussion assessment and management. *Clinics in sports medicine.* 2010;29(1):5-17.

119. Oliaro S, Anderson S, Hooker D. Management of cerebral concussion in sports: the athletic trainer's perspective. *Journal of Athletic Training.* 2001;36(3):257.

120. Lovell M. The management of sports-related concussion: current status and future trends. *Clinics in sports medicine.* 2009;28(1):95-111.

121. Mansell JL, Tierney RT, Higgins M, McDevitt J, Toone N, Glutting J. Concussive signs and symptoms following head impacts in collegiate athletes. *Brain injury.* 2010;24(9):1070-1074.

122. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *Jama.* 2003;290(19):2549-2555.

123. Corbin-Berrigan LA, Gagnon I. Postconcussion Symptoms as a Marker of Delayed Recovery in Children and Youth Who Recently Sustained a Concussion: A Brief Report. *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine.* 2016.

124. Corwin DJ, Zonfrillo MR, Master CL, et al. Characteristics of prolonged concussion recovery in a pediatric subspecialty referral population. *The Journal of pediatrics.* 2014;165(6):1207-1215.

125. Nelson LD, Tarima S, LaRoche AA, et al. Preinjury somatization symptoms contribute to clinical recovery after sport-related concussion. *Neurology.* 2016;86(20):1856-1863.

126. Bock S, Grim R, Barron TF, et al. Factors associated with delayed recovery in athletes with concussion treated at a pediatric neurology concussion clinic. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery.* 2015;31(11):2111-2116.

127. Balasundaram AP, Sullivan JS, Schneiders AG, Athens J. Symptom response following acute bouts of exercise in concussed and non-concussed individuals - a systematic narrative review. *Physical therapy in sport : official journal of the Association of Chartered Physiotherapists in Sports Medicine.* 2013;14(4):253-258.

128. Cavanaugh JT, Guskiewicz KM, Giuliani C, Marshall S, Mercer V, Stergiou N. Detecting altered postural control after cerebral concussion in athletes with normal postural stability. *British journal of sports medicine.* 2005;39(11):805-811.

129. Cavanaugh JT, Guskiewicz KM, Stergiou N. A nonlinear dynamic approach for evaluating postural control. *Sports Medicine.* 2005;35(11):935-950.

130. Guskiewicz KM. Balance assessment in the management of sport-related concussion. *Clinics in sports medicine.* 2011;30(1):89-102.

131. Shaw NA. The neurophysiology of concussion. *Progress in neurobiology.* 2002;67(4):281-344.

132. Guskiewicz KM, Perrin DH, Gansneder BM. Effect of mild head injury on postural stability in athletes. *Journal of Athletic Training.* 1996;31(4):300.

133. Parker TM, Osternig LR, Van Donkelaar P, Chou L. Gait stability following concussion. *Medicine and science in sports and exercise.* 2006;38(6):1032.

134. 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. *Clinical Neurophysiology.* 2008;119(2):281-289.

135. Susco TM, McLeod TCV, Gansneder BM, Shultz SJ. Balance recovers within 20 minutes after exertion as measured by the Balance Error Scoring System. *Journal of athletic training.* 2004;39(3):241.

136. Echemendia RJ, Putukian M, Mackin RS, Julian L, Shoss N. Neuropsychological test performance prior to and following sports-related mild traumatic brain injury. *Clinical Journal of Sport Medicine.* 2001;11(1):23-31.

137. Broglio SP, Sosnoff JJ, Ferrara MS. The relationship of athlete-reported concussion symptoms and objective measures of neurocognitive function and postural control. *Clinical Journal of Sport Medicine.* 2009;19(5):377-382.

138. Broglio SP, Macciocchi SN, Ferrara MS. Sensitivity of the concussion assessment battery. *Neurosurgery.* 2007;60(6):1050-1058.

139. Register-Mihalik JK, Guskiewicz KM, Mihalik JP, Schmidt JD, Kerr ZY, McCrea MA. Reliable change, sensitivity, and specificity of a multidimensional concussion assessment battery: implications for caution in clinical practice. *The Journal of head trauma rehabilitation.* 2013;28(4):274-283.

140. Belanger HG, Vanderploeg RD. The neuropsychological impact of sports-related concussion: a meta-analysis. *Journal of the International Neuropsychological Society.* 2005;11(04):345-357.

141. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2006;61(11):1166-1170.

142. Erickson K, Raji C, Lopez O, et al. Physical activity predicts gray matter volume in late adulthood The Cardiovascular Health Study. *Neurology.* 2010;75(16):1415-1422.

143. Pereira AC, Huddleston DE, Brickman AM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences.* 2007;104(13):5638-5643.

144. Gomez‐Pinilla F, Hillman C. The influence of exercise on cognitive abilities. *Comprehensive Physiology.* 2013.

145. Leclerc S, Hussain SS, Johnston KM. DOES EXERTION MODIFY RESULTS ON THE MCGILL ABBREVIATED CONCUSSION EVALUATION (MCGILL ACE)? *Medicine & Science in Sports & Exercise.* 2002;34(5):S103.

146. Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. *Cerebral cortex.* 1991;1(1):1-47.

147. Thiagarajan P, Ciuffreda KJ, Ludlam DP. Vergence dysfunction in mild traumatic brain injury (mTBI): a review. *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists).* 2011;31(5):456-468.

148. Ventura RE, Balcer LJ, Galetta SL. The neuro-ophthalmology of head trauma. *The Lancet. Neurology.* 2014;13(10):1006-1016.

149. Brahm KD, Wilgenburg HM, Kirby J, Ingalla S, Chang C-Y, Goodrich GL. Visual impairment and dysfunction in combat-injured servicemembers with traumatic brain injury. *Optometry & Vision Science.* 2009;86(7):817-825.

150. Capó-Aponte JE, Urosevich TG, Temme LA, Tarbett AK, Sanghera NK. Visual dysfunctions and symptoms during the subacute stage of blast-induced mild traumatic brain injury. *Military medicine.* 2012;177(7):804-813.

151. Healy GB. Hearing loss and vertigo secondary to head injury. *The New England journal of medicine.* 1982;306(17):1029-1031.

152. Heitger MH, Anderson T, Jones R. Saccade sequences as markers for cerebral dysfunction following mild closed head injury. *Progress in brain research.* 2002;140:433-448.

153. Heitger MH, Anderson TJ, Jones RD, Dalrymple‐Alford JC, Frampton CM, Ardagh MW. Eye movement and visuomotor arm movement deficits following mild closed head injury. *Brain.* 2004;127(3):575-590.

154. Pardue MT, Chrenek MA, Schmidt RH, Nickerson JM, Boatright JH. Potential Role of Exercise in Retinal Health. *Progress in molecular biology and translational science.* 2015;134:491-502.

155. Glaser M, Sjaardema H. The value of the electroencephalograph in cranio-cerebral injuries. *West Surg.* 1940;48:6989-6996.

156. Leon-Carrion J, Martin-Rodriguez JF, Damas-Lopez J, Martin JM, Dominguez-Morales Mdel R. A QEEG index of level of functional dependence for people sustaining acquired brain injury: the Seville Independence Index (SINDI). *Brain injury.* 2008;22(1):61-74.

157. Gaetz M, Bernstein DM. The current status of electrophysiologic procedures for the assessment of mild traumatic brain injury. *J Head Trauma Rehabil.* 2001;16(4):386-405.

158. Evans JR, Abarbanel A. *Introduction to quantitative EEG and neurofeedback.* Elsevier; 1999.

159. Herrmann CS. Human EEG responses to 1–100 Hz flicker: resonance phenomena in visual cortex and their potential correlation to cognitive phenomena. *Experimental brain research.* 2001;137(3-4):346-353.

160. Nuwer MR, Hovda DA, Schrader LM, Vespa PM. Routine and quantitative EEG in mild traumatic brain injury. *Clinical Neurophysiology.* 2005;116(9):2001-2025.

161. Arciniegas DB. Clinical electrophysiologic assessments and mild traumatic brain injury: state-of-the-science and implications for clinical practice. *International Journal of Psychophysiology.* 2011;82(1):41-52.

162. Thornton KE, Carmody DP. Traumatic brain injury rehabilitation: QEEG biofeedback treatment protocols. *Applied psychophysiology and biofeedback.* 2009;34(1):59-68.

163. Coutin-Churchman P, Anez Y, Uzcategui M, et al. Quantitative spectral analysis of EEG in psychiatry revisited: drawing signs out of numbers in a clinical setting. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2003;114(12):2294-2306.

164. Gosselin N, Lassonde M, Petit D, et al. Sleep following sport-related concussions. *Sleep medicine.* 2009;10(1):35-46.

165. Fenton GW. The postconcussional syndrome reappraised. *Clinical EEG (electroencephalography).* 1996;27(4):174-182.

166. Montgomery EA, Fenton GW, McClelland RJ, MacFlynn G, Rutherford WH. The psychobiology of minor head injury. *Psychological medicine.* 1991;21(2):375-384.

167. Thatcher RW, North DM, Curtin RT, et al. An EEG severity index of traumatic brain injury. *The Journal of neuropsychiatry and clinical neurosciences.* 2001.

168. Thatcher RW, Walker R, Gerson I, Geisler F. EEG discriminant analyses of mild head trauma. *Electroencephalography and clinical Neurophysiology.* 1989;73(2):94-106.

169. Barr WB, Prichep LS, Chabot R, Powell MR, McCrea M. Measuring brain electrical activity to track recovery from sport-related concussion. *Brain injury.* 2012;26(1):58-66.

170. McCrea M, Prichep L, Powell MR, Chabot R, Barr WB. Acute Effects and Recovery After Sport‐Related Concussion: A Neurocognitive and Quantitative Brain Electrical Activity Study. *The Journal of head trauma rehabilitation.* 2010;25(4):283-292.

171. Prichep LS, McCrea M, Barr W, Powell M, Chabot RJ. Time course of clinical and electrophysiological recovery after sport-related concussion. *The Journal of head trauma rehabilitation.* 2013;28(4):266-273.

172. Thornton K. Improvement/rehabilitation of memory functioning with neurotherapy/QEEG biofeedback. *The Journal of head trauma rehabilitation.* 2000;15(6):1285-1296.

173. Ray WJ, Teel EF, Gay MR, Slobounov SM. Feasibility of Electroencephalography for Direct Assessment of Concussion. *Concussions in Athletics*: Springer; 2014:69-87.

174. Broglio SP, Pontifex MB, O'Connor P, Hillman CH. The persistent effects of concussion on neuroelectric indices of attention. *Journal of neurotrauma.* 2009;26(9):1463-1470.

175. Thompson J, Sebastianelli W, Slobounov S. EEG and postural correlates of mild traumatic brain injury in athletes. *Neuroscience Letters.* 2005;377(3):158-163.

176. Kozlowski KF, Graham J, Leddy JJ, Devinney-Boymel L, Willer BS. Exercise intolerance in individuals with postconcussion syndrome. *J Athl Train.* 2013;48(5):627-635.

177. Carter H, Jones AM, Doust JH. Effect of 6 weeks of endurance training on the lactate minimum speed. *Journal of sports sciences.* 1999;17(12):957-967.

178. Tabata I, Irisawa K, Kouzaki M, Nishimura K, Ogita F, Miyachi M. Metabolic profile of high intensity intermittent exercises. *Medicine and science in sports and exercise.* 1997;29(3):390-395.

179. Pendergast DR, Leddy JJ, Venkatraman JT. A perspective on fat intake in athletes. *Journal of the American College of Nutrition.* 2000;19(3):345-350.

180. Simonson DC, DeFronzo RA. Indirect calorimetry: methodological and interpretative problems. *American Journal of Physiology-Endocrinology And Metabolism.* 1990;258(3):E399-E412.

181. Ramos-Jiménez A, Hernández-Torres RP, Torres-Durán PV, et al. The respiratory exchange ratio is associated with fitness indicators both in trained and untrained men: a possible application for people with reduced exercise tolerance. *Clinical medicine. Circulatory, respiratory and pulmonary medicine.* 2008;2:1.

182. Stratmann H. Effect of exercise training on multiple respiratory variables in patients with coronary artery disease: correlation with change in exercise capacity. *Angiology.* 1991;42(12):948-956.

183. Bergman BC, Brooks GA. Respiratory gas-exchange ratios during graded exercise in fed and fasted trained and untrained men. *Journal of Applied Physiology.* 1999;86(2):479-487.

184. Jeukendrup A, Mensink M, Saris W, Wagenmakers A. Exogenous glucose oxidation during exercise in endurance-trained and untrained subjects. *Journal of Applied Physiology.* 1997;82(3):835-840.

185. Messonnier L, Denis C, Prieur F, Lacour J-R. Are the effects of training on fat metabolism involved in the improvement of performance during high-intensity exercise? *European journal of applied physiology.* 2005;94(4):434-441.

186. Jamurtas AZ, Koutedakis Y, Paschalis V, et al. The effects of a single bout of exercise on resting energy expenditure and respiratory exchange ratio. *European Journal of applied physiology.* 2004;92(4-5):393-398.

187. Guskiewicz KM, Weaver NL, Padua DA, Garrett WE. Epidemiology of concussion in collegiate and high school football players. *The American journal of sports medicine.* 2000;28(5):643-650.

188. Griesbach GS, Hovda DA, Molteni R, Wu A, Gomez-Pinilla F. Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience.* 2004;125(1):129-139.

189. Lee C-W, Cho G-H. Effect of stationary cycle exercise on gait and balance of elderly women. *Journal of physical therapy science.* 2014;26(3):431-433.

190. Medicine ACoS. *ACSM's guidelines for exercise testing and prescription.* Lippincott Williams & Wilkins; 2013.

191. DeBusk RF, Stenestrand U, Sheehan M, Haskell WL. Training effects of long versus short bouts of exercise in healthy subjects. *The American journal of cardiology.* 1990;65(15):1010-1013.

192. Sasaki JE, Hickey A, Mavilia M, et al. Validation of the Fitbit wireless activity tracker for prediction of energy expenditure. *Journal of Physical Activity and Health.* 2015;12(2):149-154.

193. Nelson MB. Activity-specific validity of several consumer-based physical activity monitors. 2015.

194. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *The Journal of head trauma rehabilitation.* 2006;21(5):375-378.

195. Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. *Journal of athletic training.* 2007;42(2):311.

196. Schneiders A, Sullivan S, Handcock P, Gray A, McCrory P. The effect of graded exercise on motor performance tasks used in the neurological assessment of sports related concussion. *Journal of Science and Medicine in Sport.* 2010;12:e42-e43.

197. Rivest L-P. Statistical properties of Winsorized means for skewed distributions. *Biometrika.* 1994:373-383.

198. Koscs M. *Effects of exertional exercise on the Standardized Assessment of Concussion (SAC) Score.* ProQuest; 2008.

199. Scheiman M, Gallaway M, Frantz KA, et al. Nearpoint of convergence: test procedure, target selection, and normative data. *Optometry and vision science : official publication of the American Academy of Optometry.* 2003;80(3):214-225.

200. Iverson GL, Lovell MR, Collins MW. Interpreting change on ImPACT following sport concussion. *The Clinical Neuropsychologist.* 2003;17(4):460-467.

201. Moore BM, Adams JT, Barakatt E. Outcomes Following a Vestibular Rehabilitation and Aerobic Training Program to Address Persistent Post-Concussion Symptoms. *Journal of allied health.* 2016;45(4):e59-e68.

202. Yu S, Yarnell J, Sweetnam P, Murray L. What level of physical activity protects against premature cardiovascular death? The Caerphilly study. *Heart.* 2003;89(5):502-506.

203. Andersen LB, Schnohr P, Schroll M, Hein HO. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. *Archives of internal medicine.* 2000;160(11):1621-1628.

204. Fransson EI, Alfredsson LS, Ulf H, Knutsson A, Westerholm PJ. Leisure time, occupational and household physical activity, and risk factors for cardiovascular disease in working men and women: the WOLF study. *Scandinavian Journal of Public Health.* 2003;31(5):324-333.

205. Teychenne M, Ball K, Salmon J. Physical activity and likelihood of depression in adults: a review. *Preventive medicine.* 2008;46(5):397-411.

206. Blomqvist CG, Saltin B. Cardiovascular adaptations to physical training. *Annual Review of Physiology.* 1983;45(1):169-189.

207. Casaburi R, Whipp BJ, Wasserman K, Beaver WL, Koyal SN. Ventilatory and gas exchange dynamics in response to sinusoidal work. *Journal of Applied Physiology.* 1977;42(2):300-301.

208. Deacon B, Abramowitz J. Fear of needles and vasovagal reactions among phlebotomy patients. *Journal of anxiety disorders.* 2006;20(7):946-960.

209. Lucía A, Hoyos J, Pardo J, Chicharro JL. Metabolic and neuromuscular adaptations to endurance training in professional cyclists: a longitudinal study. *The Japanese journal of physiology.* 2000;50(3):381-388.

210. Bloom G, Horton A, McCrory P, Johnston K. Sport psychology and concussion: new impacts to explore. *British journal of sports medicine.* 2004;38(5):519-521.

211. Reilly JJ, McDowell ZC. Physical activity interventions in the prevention and treatment of paediatric obesity: systematic review and critical appraisal. *Proceedings of the Nutrition Society.* 2003;62(03):611-619.

212. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *Journal of the American Heart Association.* 2013;2(1):e004473.

213. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *Bmj.* 2001;322(7289):763.

214. Herring MP, O'connor PJ, Dishman RK. The effect of exercise training on anxiety symptoms among patients: a systematic review. *Archives of internal medicine.* 2010;170(4):321-331.

215. Kontos AP, Collins M, Russo SA. An introduction to sports concussion for the sport psychology consultant. *Journal of Applied Sport Psychology.* 2004;16(3):220-235.

216. Smith C, Veenhuis P, Meyer R. Traumatic brain injury. North Carolina's challenge. *NC Med J.* 2001;62(6):328-334.

217. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain research reviews.* 1999;29(2):169-195.

218. Löwe B, Decker O, Müller S, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Medical care.* 2008;46(3):266-274.

219. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine.* 2006;166(10):1092-1097.

220. Kroenke K, Spitzer RL, Williams JB. The Phq‐9. *Journal of general internal medicine.* 2001;16(9):606-613.

221. Martin A, Rief W, Klaiberg A, Braehler E. Validity of the brief patient health questionnaire mood scale (PHQ-9) in the general population. *General hospital psychiatry.* 2006;28(1):71-77.

222. Barry RJ, Clarke AR, Johnstone SJ, Magee CA, Rushby JA. EEG differences between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology.* 2007;118(12):2765-2773.

223. Lagopoulos J, Xu J, Rasmussen I, et al. Increased theta and alpha EEG activity during nondirective meditation. *The Journal of Alternative and Complementary Medicine.* 2009;15(11):1187-1192.

224. Mathersul D, Williams LM, Hopkinson PJ, Kemp AH. Investigating models of affect: relationships among EEG alpha asymmetry, depression, and anxiety. *Emotion.* 2008;8(4):560.

225. Cavanagh JF, Shackman AJ. Frontal midline theta reflects anxiety and cognitive control: meta-analytic evidence. *Journal of Physiology-Paris.* 2015;109(1):3-15.

226. Corsi-Cabrera M, Solis-Ortiz S, Guevara MA. Stability of EEG inter- and intrahemispheric correlation in women. *Electroencephalogr Clin Neurophysiol.* 1997;102(3):248-255.

227. Corsi-Cabrera M, Galindo-Vilchis L, del-Río-Portilla Y, Arce C, Ramos-Loyo J. Within-subject reliability and inter-session stability of EEG power and coherent activity in women evaluated monthly over nine months. *Clinical Neurophysiology.* 2007;118(1):9-21.

228. McEvoy L, Smith M, Gevins A. Test–retest reliability of cognitive EEG. *Clinical Neurophysiology.* 2000;111(3):457-463.

229. Salinsky MC, Oken BS, Morehead L. Test-retest reliability in EEG frequency analysis. *Electroencephalogr Clin Neurophysiol.* 1991;79(5):382-392.

230. van Donkelaar P, Langan J, Rodriguez E, et al. Attentional deficits in concussion. *Brain injury.* 2005;19(12):1031-1039.

231. Field M, Collins MW, Lovell MR, Maroon J. Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. *The Journal of pediatrics.* 2003;142(5):546-553.

232. Schmidt M, Kanda P, Basile L, et al. Index of alpha/theta ratio of the electroencephalogram: a new marker for Alzheimer's disease. *Frontiers in aging neuroscience.* 2013;5:60.

233. Tinius TP, Tinius KA. Changes after EEG biofeedback and cognitive retraining in adults with mild traumatic brain injury and attention deficit hyperactivity disorder. *Journal of Neurotherapy.* 2000;4(2):27-44.

234. Gagnon I, Swaine B, Forget R. Using activity diaries to measure children's and adolescents' compliance with activity restrictions after mild traumatic brain injury. *The Journal of head trauma rehabilitation.* 2009;24(5):355-362.