Title: Neuroplastic Mechanisms Underlying Augmented Neuromuscular Training

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PROTOCOL TITLE: Neuroplastic Mechanisms Underlying Augmented Neuromuscular Training

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National Institutes of Health

1. Study Summary

Study Title	Neuroplastic Mechanisms Underlying Augmented Neuromuscular Training
Study Design	Randomized Controlled Trial
Primary Objective	To determine the neural mechanisms of acquisition of injury-resistant movement from augmented neuromuscular training
Secondary Objective(s)	To determine the neural mechanisms for injury-resistant movement pattern transfer to VR-simulated sport.
Research Intervention(s)/Interactions	Intervention (Augmented Neuromuscular Training) as described in parent study Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality
Study Population	Adolescent Female Athletes
Sample Size	Up to 120 athletes
Study Duration for individual participants	Approximately 6 weeks-4months (includes up to 2 study visits)
Study Specific Abbreviations/ Definitions	Augmented Neuromuscular Training (aNMT)
Funding Source (if any)	National Institutes of Health

2. Objectives

The purpose of this proposal is to determine the neural mechanisms of augmented neuromuscular training (aNMT).

The objective of the current proposal is to utilize our neuroimaging breakthroughs to identify the neural mechanisms responsible for neuromuscular training-induced sensorimotor adaptation and transfer of injury-resistant movement patterns to sport. Our preliminary data indicate that training related neural sensory integration activity supports efficient motor cortex activity which promotes the transfer of injury-resistant movement patterns.[26,30-34]

3. Background

Anterior cruciate ligament (ACL) injury is a common and debilitating knee injury affecting over 350,000 children or young adults each year, drastically reducing their chances for an active and healthy life.[1-3] ACL injury has a substantial negative impact on individuals and society including direct costs up to $13 billion annually.[4,5] Long-term indirect costs far exceed that amount, as ACL injury is linked to accelerated development of disabling osteoarthritis within a few years after injury.[6,7] The onset of osteoarthritis after ACL injury, combined with a 1 in 4 risk of a subsequent

ACL injury, has led the National Public Health Agenda for Osteoarthritis to strongly recommend expansion and refinement of injury prevention strategies.[8,9] However, the current standard of care for ACL injury prevention, has not decelerated the trajectory of increased non-contact ACL injury rates in susceptible female athletes.[1,10-12] Despite extensive efforts, the efficacy of neuromuscular training has not advanced with ~100 patients still requiring treatment to prevent a single ACL injury.[10,13] Current ACL injury prevention programs can improve isolated knee joint injury risk mechanics (knee abduction motion & loading) during standard testing in the lab,[14-21] but may be inadequate for the transfer of global injury-resistant movement patterns during demanding functional tasks,[22,23] limiting translation to sport. Limited transfer of injury-resistant movement patterns likely explains how motor coordination related non-contact ACL injuries still occur despite current best-practice interventions.[24] If injury prevention programs fail to induce adaptation and transfer to sport scenarios, injury risk will not be mitigated no matter how well executed the intervention or compliant the participants.[22,23,25] A missing link for improving efficacy is a comprehensive understanding of the neural mechanisms by which the nervous system adapts and transfers injury-resistant movement patterns to new environments (i.e., from the intervention to sport).[26-28]

Limitations in measuring brain activity associated with the sensorimotor control of dynamic lower extremity movements have been the main barrier to identifying the neural mechanisms underlying the adaptation and transfer of injury-resistant movement patterns. We have overcome this barrier by developing novel neuroimaging paradigms of functional lower extremity movements that engage the fundamental sensorimotor capabilities of knee position and force control underpinning injury-resistant movement control.[25,29] The objective of the current proposal is to utilize our neuroimaging breakthroughs to identify the neural mechanisms responsible for neuromuscular training-induced sensorimotor adaptation and transfer of injury-resistant movement patterns to sport. Our preliminary data indicate that training related neural sensory integration activity supports efficient motor cortex activity which promotes the transfer of injury-resistant movement patterns.[26,30-34]

Summary of Prior Work

We have successfully collected data at Cincinnati Children's Hospital Medical Center using our functional knee motor tasks on healthy female participants (Study, Effects of Neuromuscular Training on EEG Adaptations in Young Athletes; PI Gregory Myer and Study, Novel Protection against Potential Brain Injury during Competitive Non-helmeted Sport in Females; PI Gregory Myer). Our preliminary work demonstrated efficacy in collecting the data while minimizing head motion and establishing reliability across testing sessions. Head motion was limited to .23-.43 mm of absolute motion and .06-.11 mm of relative head motion across all tasks. Intraclass correlation coefficients demonstrated high between session reliability (ICC: .82-.94) for primary motor cortex mean for all tasks (n = 13). Participants have reported no problems with the tasks and the majority have returned for subsequent testing.

4. Study Endpoints

The post-training study visit is the study's primary endpoint.

5. Study Intervention/Investigational Agent

As described in parent study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality" innovative augmented neuromuscular training (aNMT) techniques will be used to enhance sensorimotor learning and reduce biomechanical risk factors for ACL injury. aNMT integrates biomechanical screening with state-of-the-art augmented reality headsets to display real-time feedback that maps complex biomechanical variables onto simple visual feedback stimuli that participants "control" via their own movements.

6. Procedures Involved

Study Design

Enrolled participants will complete MRI testing pre- and post-aNMT (which is a component of parent study: "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality" and is required to be completed to fully participate in the present study). All MRI scanning will be performed on GE SIGNA™ Premier 3.0 Tesla MR scanners in the EMORY Sports Performance and Research Center (SPARC), located at the Atlanta Falcons' Flowery Branch NFL headquarters and practice facility. Sedation will not be used for any of the test visits. The entire MRI protocol may include high resolution T1-weighted 3D images, a 61 direction diffusion tensor imaging sequence, resting state fMRI, and task-based fMRI. The task-based fMRI will be focused on motor function, participants will be asked to complete lower extremity movements including knee flexion and extension (see image below) and a combined hip and knee flexion and extension. The MR scan will be completed in 90 minutes or less. Peripheral pulse oximetry and respiration waveforms may also be collected for data analysis in order to minimize the potential confounding effect from the physiological changes. Biomechanics data of the leg segments may be collected using a custom designed MRI safe motion capture system . Reflective markers compatible with MRI system may be attached to the subject's thighs and shanks using Velcro straps as seen in image below. A practice session of the fMRI paradigms will be completed just prior to scanning to allow the participant to ask any questions and be familiar with the protocol.

Study Procedures

Anthropometrics

Height and weight will be collected. Hand and leg dominance will be asked based on the two questions of, which hand does the participant write with and which foot does the participant use to kick a ball.

Questionnaires

A series of non-invasive questionnaires pertaining to general health history, physical activity, and knee pain may be administered including a general demographics questionnaire, the International Physical Activity Questionnaire short form (IPAQ_short), and the Movement Imagery Questionnaire-3 (MIQ-3). The MIQ-3 is a 12-item questionnaire that assesses an individual's ability to imagine four movements using: 1) Internal visual imagery 2) External visual imagery and 3) Kinesthetic imagery. The MIQ-3 can quantify motor imagery dominance for the athletes enrolled in the present study.

Subjects may also be asked, "Have you ever been diagnosed with patellofemoral pain." If yes, subjects will also complete the following knee pain questionnaires: Anterior Knee Pain Scale (AKPS), shortened knee pain scale, the Tampa Scale Kinesiophobia (TSK) questionnaire, and the International Knee Documentation Committee (IKDC) scale. If subjects answer no, they will complete the same knee pain questionnaires, but will complete the Tampa Scale Kinesiophobia General (TSK-G; used for pain free controls) instead of the TSK.

All questionnaires may be administered via Redcap surveys during each study visit.

Flanker Test

Participants may also complete the Flanker Test. The flanker test is a non-invasive, 7-minute computer based task that measures response inhibition by assessing visual-motor responsiveness. Specifically, a series of stimuli (arrows) are presented that are congruent (same

direction) or incongruent (different) with a target stimuli (visual) that a participant must respond to (key press) as quickly and accurately as possible (motor response) for testing their visual-motor capability. Including this test will provide an opportunity to gather prospective data regarding participants' visual-motor capability that can be associated with changes in brain activity following augmented neuromuscular training. Specifically, exploratory analyses will use these data as behavioral correlates (or covariates) in the neuroimaging analyses and/or for sub-group analyses based on inter-individual differences in visual-motor capability.

Trail Making Test

Participants may also complete the Trail Making test, which is a computer/tablet based task in which participants connect dots as quickly as they can with minimizing errors. This task provides visual motor capability data to supplement that of the Flanker Test.

MR imaging data Acquisition:

Magnetic Resonance Imaging (MRI), are all based on the concept of using magnetic fields and radio waves to make chemical, anatomical and physiological assessments with in the living tissue. This technology has been utilized for diagnostic and research purposes since the early 1980s.

Participants will be allowed to communicate with the MR operator via an always-on, two-way intercom at any time. In addition, the participants have a hand-held air ball to squeeze in the event that they elect to be removed from the magnet immediately. The study participants have control over their presence in the magnet, which in turn tends to minimize feelings of claustrophobia. As magnetic resonance imaging employs the use of strong magnets, patients will receive a standard preoperative screening questionnaire regarding the potential for ferromagnetic objects within their bodies to ensure their safety during the study. Participants will be screened via Emory's Department of Radiology and Imaging Sciences standard procedures and forms for MRI specific contraindications such as:

- Braces or permanent metal dental work
- Insulin pump
- Cardiac pacemaker
- Cochlear implants
- Hearing aids
- Aneurysm clips
- Orthopedic pins, wires, screws, or plates
- Possible pregnancy
- Any other exclusionary criteria as documented on the standard MRI patient screening forms, completed by the imaging technicians at each study visit.

Testing will consist of two MRI sessions (approximately 6 weeks-4 months apart) using the GE SIGNA™ Premier 3.0 Tesla MR scanners in the EMORY Sports Performance and Research Center (SPARC). During the acquisition of MR images, the study participants will lie on the scanner table. For most portions of MR acquisition, the study participants will only be instructed to lie still. For other parts of the acquisition, study participants will be asked to complete a knee

flexion/extension task and a combined knee and hip flexion/extension movement while keeping the rest of their body still. Peripheral pulse oximetry and respiration waveforms may also be collected for data analysis in order to minimize the potential confounding effect from the physiological changes. A practice session of the fMRI paradigms will be completed just prior to scanning to allow the participant to ask any questions and be familiar with the protocol. Each MR scan will be completed in 90 minutes or less. If participants withdraw from the parent study, "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality" or do not complete the aNMT program, they may not be eligible to complete the post-training MRI session for this study.

In the event that technical issues arise during an MRI and the entire scan session is not able to be completed, a participant may be asked to return to complete the session once the technical issue has been resolved. In this event, the participant will be compensated accordingly for both visits. Every effort will be made to re-schedule the appointment; however, there may not be an option to re-schedule due to time constrictions or participant schedule conflicts. If this occurs then the tests not administered due to technical issues will be considered as lost for analysis.

If an enrolled participant sustains a lower extremity or concussion injury, she may repeat all tests performed at the pre-training appointment as well as the opportunity to participate in longitudinal follow-up brain fMRIs and joint specific structural imaging. The brain fMRI paradigms will be identical to the current protocol. All movements will be monitored for patient pain or discomfort and not completed if patient reports unacceptable pain. Additionally, to further evaluate neuroplasticity associated with injury, anatomical/structural MRI sequence may be completed during study visits. The structural MRI may include relevant sequences such as coronal proton-density imaging, T2 mapping, T1 weighted, T1 rho. The structural MRIs may be repeated or captured simultaneously on the non-injured limb for comparative purposes regarding the time course of healing. The additional structural MRI sequences would not last more ~45 minutes.

7. Data and Specimen Banking

N/A

8. Sharing of Results with Participants

Results of the study will not be directly shared with participants unless clinically significant abnormalities are found as outlined below. This study will be registered as required on the clinicaltrials.gov website which participants can view information; such as results, when they are updated.

Anatomic imaging obtained as part of this study will be reviewed by a board-certified radiologist for any potentially clinically significant abnormalities according to processes outlined by Emory's Department of Radiology and Imaging Sciences. The Radiologist will notify the participant's primary care physician, participant or the participant's parent/legal guardian (if participant is

under the age of 18) if we see such an incidental finding. Depending on the type of incidental finding, we may contact the participant by mail or by phone. The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study.

9. Study Timelines

Each participant will participate in two planned study visits that each may take up to 3 hours. Study visit one will occur as soon as possible after enrolling in IRB study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality" and study visit 2 will be completed as soon as possible following the conclusion of IRB study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality" (approximately 6 weeks-4 months apart). It is expected that enrollment will take up to 2 years to complete. Data analysis will continue for up to a 2 year period following the final enrollment.

10. Inclusion and Exclusion Criteria

We aim to recruit up to 120 healthy female volunteers who are enrolled in parent study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality". Participants interested in participating in "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality" will be given the opportunity to also participate in this study. As part of the recruitment for "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality", interested participants complete an online interest form, which is maintained in REDCap. We have included additional questions with regard to interest in also participating in this study, along with pre-screening questions which would identify interested participants who are potentially ineligible for this study due to contraindications of the MRI (i.e. orthodontic braces or other known metal in the body). Once REDcap interest forms are submitted by participants/parents, those interested and eligible for this study will be contacted by our study team with more information. The participants and parents/guardians (if participant is under the age of 18) who voluntarily agree to participate will be scheduled to complete the pre-participation testing.

Inclusion criteria

- Enrolled in IRB study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality"
  - This can include individuals who are minors and any additional inclusion criteria outlined in the study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality"
- No contraindications to MRI as identified by Emory's Department of Radiology and Imaging Sciences standard screening procedure/form completed by the imaging technicians at each study visit

Exclusion criteria

- Any contraindications to MRI as identified by Emory's Department of Radiology and Imaging Sciences standard screening procedure/form completed by the imaging technicians at each study visit
- If **not** enrolled in IRB Study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality"

11. Vulnerable Populations

This study is no greater than minimal risk, as the testing procedures and training intervention have been utilized in children/adolescents. Both the child and the parent/legal guardian will be involved in the consent process prior to participation

12. Local Number of Participants

We aim to recruit up to 120 healthy female volunteers who are enrolled in parent study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality".

13. Recruitment Methods

Participants interested in participating in "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality" will be given the opportunity to also participate in this study. Potential subjects may be sent a link to an online recruitment video. As part of this link, a recruitment video will be embedded on the landing page that gives more general information about the study and participation. As part of the recruitment for "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality", interested participants complete an online interest form, which is maintained in REDCap. We have included additional questions with regard to interest in also participating in this study, along with pre-screening questions which would identify interested participants who are potentially ineligible for this study due to contraindications of the MRI (i.e. orthodontic braces or other known metal in the body). Once REDcap interest forms are submitted by participants/parents, those interested and eligible for this study will be contacted by our study team with more information. The participants and parents/guardians (if participant is under the age of 18) who voluntarily agree to participate will be scheduled to complete the pre-participation testing. All recruitment documents/forms that will be utilized for this study have been submitted under the parent "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality".

Compensation

Participants will be compensated for their time and effort in participating in this study. They will receive a $50 Clincard Mastercard® gift card for completing session one and a $100 Clincard Mastercard® gift card for completing session two. Participation in session two (post-training) is contingent upon completion of the augmented neuromuscular training program. Registration in the Clincard payment system requires a social security number, which will be acquired via a

complete W-9 form for each participant. Participants will be compensated even if they are not able to complete the entire MRI session.

14. Withdrawal of Participants

Enrolled participants must also remain enrolled in parent study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality". If a participant withdraws from study "Real-time Sensorimotor Feedback for Injury Prevention Assessed in Virtual Reality" prior to their post-training visit then they will no longer be eligible to complete their study visit and will be automatically withdrawn from this study. Participants will be made aware of eligibility criteria to enroll and remain enrolled in this study during the consent process.

If any participant decides to withdraw for their own reasons, they may do so at any time during the study. We may ask the participant why they chose to withdraw from the study, but they are not required to provide an explanation. Any data or information collected prior to withdraw, may still be used for study purposes. Participants will be made aware of this information during the consent process. They will also be made aware that their study participation is 100% voluntary and that they may choose to withdraw from the study at any time

15. Risks to Participants

MR Imaging of the Brain

The risk the magnetic fields and the strengths, and radio waves is vanishingly small. There is a small chance that some patients can experience anxiety from the confined space of the magnet's bore. Another minor concern when using magnetic resonance technology is the noise the magnet makes when collecting data. Noise abatement measures are used; headphones and music with a selection of music options. Ferrous implants and or piercings can be affected in the magnetic field. Therefore, participants will be advised to remove these and or scanned with a metal detector to screen for such objects.

Our colleague's previous experience with MRI experiments has provided confidence that there should be no psychological, physical, legal, or social risks involved with MRI experiments in general, though participants may be anxious about the scan, possibly causing them slight stress. MRI does not involve ionizing radiation and scans up to 8 T are considered as non-significant risk. The risks common to all MRI scans can be described as: (1) ferromagnetic objects introduced into the magnetic field, (2) confinement in the scanner bore, (3) radio-frequency (RF) heat deposition in tissue which is monitored by the system to conform with FDA guidelines, and (4) acoustic noise. These risks are addressed below: Participants are allowed to communicate with the MR operator via an always-on, two-way intercom at any time. In addition, the participants have a hand-held air ball to squeeze in the event that they elect to be removed from the magnet immediately. Thus, the participants have control over their presence in the magnet, which in turn tends to minimize feelings of claustrophobia.

Anatomic imaging obtained as part of this study will be reviewed by a board-certified radiologist for any potentially clinically significant abnormalities according to processes outlined by Emory's Department of Radiology and Imaging Sciences. The Radiologist will notify the participant's primary care physician, participant or the participant's parent/legal guardian (if participant is under the age of 18) if we see such an incidental finding. Depending on the type of incidental finding, we may contact the participant by mail or by phone. The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study.

Data Storage

There is also a minimal risk that the data collected for each participant may be viewed by individuals outside the research team. The risk that confidential data may be viewed is relevant for both the written forms and electronic databases. Precautions, such as password-protected computers, locked cabinets and coded identification numbers, are in place to minimize this risk.

Adverse Events

If a participant believes they have sustained an injury as a result of the study then they are instructed to contact the principal investigator or lead coordinator who in turn will then contact Emory's IRB and necessary funding institutions, as aforementioned. If a participant sustains an injury during testing they will be referred to the most appropriate medical facility or seek medical attention by the physician/medical specialist of their choice.

16. Potential Benefits to Participants

Participants of this study will not receive any direct or immediate benefits by completing this study.

17. Compensation to Participants

Participants will be compensated for their time and effort in participating in this study. They will receive a $50 Clincard Mastercard® gift card for completing session one and a $100 Clincard Mastercard® gift card for completing session two. Participation in session two (post-training) is contingent upon completion of the augmented neuromuscular training program. Registration in the Clincard payment system requires a social security number, which will be acquired via a complete W-9 form for each participant. Participants will be compensated even if they are not able to complete the entire MRI session.

18. Data Management and Confidentiality

Data Analysis

Data processing and analysis will be performed using a series of existing software including FSL (FMRIB's Diffusion Toolbox in FSL Software, Oxford, UK), AFNI (Cox, 1996) , SPM (Statistical Parametric Mapping analysis package, Wellcome Department of Cognitive Neurology, London, UK), DTIStudio (John Hopkins University, Baltimore, MD; Jiang et al., 2006), as well as additional customized software written in Matlab or IDL.

Functional fMRI (resting state fMRI) will also be subjected to routine image pre-processing pipeline. Functional connectivity analysis will be performed, using the CONN toolbox, http://www.nitrc.org/projects/conn/) between all brain regions that are involved in the proper functioning of default mode network, sensory motor network, visual network, and a series of other networks that are known to be strongly functionally connected during resting state.

Biomechanics data will be post processed to calculate leg angle in the during biomechanics and VR tasks. Joint angle data will be analyzed across population to ensure uniformity in task objective fulfilment. All analysis will be performed using customized software in Matlab.

Data Storage

A coded identification number will be used to track all collected data. Data will be stored on password-protected computers and only pertinent research personnel will have access. Data forms will be stored by coded identification number in a locked cabinet to which only pertinent research personnel have access. All data will be collected for research purposes only. Data (other than MRI imaging files/data) may be maintained via a REDCap database with only pertinent research personnel being granted access.

Additional Data Analysis and Storage Information

If additional analyses are needed necessitating data transfer to staff at Ohio University, we will provide secure de-identified transfer of data for post-processing and analysis, only. Specifically, neuroimaging and associated behavioral data (e.g., demographics and questionnaires) to support the analytics would be shared via Microsoft one drive. No identifiable information will be shared or removed from Emory's secure data storage by Ohio University personnel. Dustin Grooms is a Co-Investigator on this NIH funded project and he and his personnel at Ohio University possess unique skillsets that align with this project specific to the neuroimaging analyses with functional motor tasks.

19. Provisions to Monitor the Data to Ensure the Safety of Participants

Dr. Philip Wong will serve as a study monitor for this project for any incidental findings, while the PI and study coordinators will be responsible for monitoring data quality and adverse events. The monitor will review adverse events and unanticipated events at the time they occur and will report his assessment of the event(s) to the PI. This research study involves only minimal risk for participants.

20. Provisions to Protect the Privacy Interests of Participants

The participant has the right to privacy. The investigators will protect participant privacy to the extent allowed by law. All facts about this study that can describe a participant's name will be

kept private. Results of the study will be summarized regarding age, etc. but the investigators will take every precaution necessary to keep names private.

To maintain the privacy information of study participants, only pertinent research personnel will have access to participant information. Research personnel are employees of Emory and have been trained in human participant's research and HIPAA compliance. To further ensure privacy, all data will be analyzed and tracked using a coded identification number that does not use identifiable personal information. Personal information and identifiers will be securely recorded and filed by the administrative assistant/study coordinators. The data will be encrypted with a password and stored on a personal computer and backed up on a network drive. The participant identification code will be used on all data questionnaires.

The results of this study will be kept confidential. No participant identification will be made public record in any form unless the participant gives his or her expressed written permission of release of participant's name, photograph or likeness captured on video. The investigators will be available for any questions that may arise.

21. Economic Burden to Participants

N/A

22. Consent Process

A potential participant will be contacted by a study coordinator as outlined by our recruiting process. Once potential participants and parents/guardians (if participants are under the age of 18) voluntarily agree to participate they will be scheduled to complete the pre-participation testing and the process of consent can begin. The IRB approved consent form may be sent to the participant/parent/guardian prior to the process of consent taking place in order to give them ample time to review the study. A study coordinator will review the informed consent and the participant/parent/guardian will have the opportunity to ask any questions regarding the study and/or the study protocol. The participant/parent/guardian will be given time to decide whether or not they wish to participate and if so, asked to sign the informed consent. Once the signature is obtained, the participant/parent/guardian will be given a copy of the consent and testing will commence. At no time will the participant be coerced into participation and they will be reminded their participation is always 100% voluntary and that they can drop the study at any time. Receiving the informed consent prior to enrollment can also allow the participants to review the study information prior to participating in the study. This will aid the participant to make an informed, unforced decision regarding election to participate in the study.

We will be using a single consent form to consent and assent (if participant is under the age of 18) the participant, the parent/guardian, and any adult participants (participant that is 18 or older). The participants will be given adequate time to review the study materials and ask questions. If they choose to participate, the participant and parent/guardian will sign the IRB

approved consent forms. If a participant turns 18 while participating in the study, then they will be re-consented as an adult as soon as possible.

Due to the study only being minimal risk, only one parent/guardian is needed to sign the consent form for a participant that is under the age of 18. In the event that a parent or guardian will not be present at the scheduled testing appointment, consent/assent forms will be provided ahead of time for review and the parent/guardian may be contacted by phone to go over the consent in its entirety prior to the participants' study visit. If the parent/guardian agrees for their child to participate then they can sign the consent form and scan/fax the form to a study coordinator prior to the child's scheduled study visit or they can send the signed consent form with the child to the study visit. Due to the process of consent possibly occurring prior to the study visit, dates on the consent form from a parent/guardian may be different then their child's date of consent. The assigned study coordinator will ensure that consents are always done thoroughly allowing time for questions and review and that all necessary forms have been signed and dated prior to any data collection.

23. Setting

The research activities will take place at Emory's Sport Performance and Research Center (SPARC) located at the Flowery Branch facility. The SPARC contains all of the necessary space, equipment, and technology for this research project.

Imaging resources at SPARC include access to two ultra-high-performance imaging instruments dedicated exclusively to Sports Medicine research and clinical activities. The GE SIGNA™ Premiers located in SPARC, are 70-cm, 3.0-T systems. These magnets feature an actively shielded, zero boil-off design and supports 50(X) × 50(Y) × 50(Z)cm FOV imaging. The SuperG Gradient Coil Technology can achieve 80mT/m amplitude & 200 T/m/s slew rate, and support 2nd order shim terms. Hollow, direct water cooling helps dissipate heat from the gradient coils and improves the duty cycle. The Premier system also features 146 receiver channels with dedicated direct digital A/D converters, with 2-channel PTx architecture for MultiDrive RF shimming. AIR technology is employed in the RF coils, which weighs 66% lighter on the patients. The AIR technology also provides reliability and flexibility to patient positioning, and this technology is included in the 48-channel head coil, 30-channel anterior array, and 60-channel embedded Posterior Array. The system is also fully equipped with specialized coils such as Small anterior array, 16ch T/R Hand Wrist Array, 8ch Foot/Ankle Array, Flex Coil suite.

Biomechanics with Imaging: Each MRI is also outfitted with 8 shielded cameras (7 optoelectronic marker based cameras and one monochrome reference video camera, supporting marker based as well as markerless capture for enhanced tracking) for an MRI-compatible 3D motion analysis system to support the aims of the current project.

24. Resources Available

The PI of this study will ensure that all study staff will have proper training (protocol, responsibilities, CITI, etc.) in order to properly perform any assigned duties and functions on this human subjects research study. All other resources available for this study have been outlined accordingly throughout the protocol.

Personnel Resources:

Investigators from Ohio University (Grooms, Co-PI) will be on-site at Emory and assisting with MRI data collection.

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