

**STUDY TITLE: Neuroplastic Mechanisms Underlying Augmented Neuromuscular Training**

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**CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER****STUDY TITLE:** Neuroplastic Mechanisms Underlying Augmented Neuromuscular Training**INVESTIGATOR INFORMATION:**

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**(1) ABSTRACT:**

Anterior cruciate ligament (ACL) injury is a common activity-related knee injury with a substantial negative impact on individuals and society. Annual direct costs exceed \$13 billion, and the long-term indirect costs far exceed that figure, as ACL injury is also linked to accelerated development of disabling osteoarthritis within a few years after injury. The National Public Health Agenda for Osteoarthritis recommends expanding and refining evidence-based ACL injury prevention to reduce this burden. We have identified modifiable risk factors that predict ACL injury in young female athletes. Our neuromuscular training targets those factors and shows statistical efficacy in high-risk athletes, but meaningful transfer of low-risk mechanics to the field of play has been limited, as current approaches are not yet decreasing national ACL injury rates in young female athletes. The key gap is how to target mechanisms that allow transfer of risk-reducing motor control strategies from the intervention to the athletic field. The mechanisms that ultimately make such transfer possible are neural, but thus far injury prevention training focusing on neuromuscular control has not utilized neural outcomes. Our published and new preliminary data on neuroplasticity related to injury and neuromuscular training demonstrate our proficiency to capture these neural outcomes and future capability to target these neural mechanisms to improve the rate of motor transfer. The data support this proposal's central hypothesis that increased sensory, visual and motor planning activity to improve motor cortex efficiency is the neural mechanism of adaptation transfer to realistic scenarios. The ability to target the neural mechanisms to increase risk-reducing motor transfer from the clinic to the world could revolutionize ACL injury prevention. The transformative, positive impact of such innovative strategies will enhance the delivery of biofeedback to optimize training and increase the potential for sport transfer. This contribution will be significant for ACL injury prevention and associated long-term sequelae in young females. This unique opportunity to enhance ACL injury prevention by targeting neural mechanisms of neuromuscular adaptation and transfer will reduce the incidence of injuries that cause costly and long-term disabling osteoarthritis.

**(2) PURPOSE:**

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

**(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.<sup>1-3</sup> ACL injury has a substantial negative impact on individuals and society including

direct costs up to \$13 billion annually.<sup>4,5</sup> 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.<sup>6,7</sup> 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.<sup>8,9</sup> 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.<sup>1,10-12</sup> Despite extensive efforts, the efficacy of neuromuscular training has not advanced with ~100 patients still requiring treatment to prevent a single ACL injury.<sup>10,13</sup> Current ACL injury prevention programs can improve isolated knee joint injury risk mechanics (knee abduction motion & loading) during standard testing in the lab,<sup>14-21</sup> but may be inadequate for the transfer of global injury-resistant movement patterns during demanding functional tasks,<sup>22,23</sup> 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.<sup>24</sup> 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.<sup>22,23,25</sup> 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).<sup>26-28</sup>

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.<sup>25,29</sup> 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.<sup>26,30-34</sup>

### **Summary of Prior Work**

A. We have successfully collected data using our functional knee motor tasks on healthy female participants (Study ID: 2014-2585; PI Gregory Myer and Study ID: 2016-0988; 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 DESIGN:**

Participants will complete MRI testing pre and post neuromuscular training (the neuromuscular training is a component of IRB study: 2014-2946 and is required to be completed to fully

participate in the present study). All MRI scanning will be performed on 3 Tesla Philips MRI scanners (3T Achieva in R-Building and 3T1 and 3T2 Ingenia in T-Building) located in Imaging Research Center (IRC) in the Cincinnati Children's Hospital Research Foundation (CCHRf). Sedation will not be used for any of the test visits. The entire MRI protocol will include high resolution T1-weighted 3D images, a 61 direction diffusion tensor imaging sequence, resting state fMRI, and task-based fMRI. The fMRI tasks 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 75 minutes or less. Peripheral pulse oximetry and respiration waveforms will 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.



##### **(5) DURATION:**

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 2014-2946 and study visit 2 will be completed as soon as possible following the conclusion of IRB study 2014-2946 (approximately 6-8 weeks apart). Data analysis will continue for a 2 year period following the final enrollment.

##### **(6) SELECTION & RECRUITMENT OF PARTICIPANTS**

We aim to recruit approximately 120 healthy female volunteers who enroll in Study #2014-2946. Participants are recruited from local school districts local sports clubs and teams, local colleges, adult sport leagues, and professional sports teams, through our well established network with area coaches and athletic trainers. Questions regarding participation will be answered during the presentations or through e-mail or phone. Participants will be contacted via telephone to further explain the study, answer any additional questions and to enroll them in the study. The

participants and parents/guardians (if subject under age of 18) who voluntarily agree to participate will be scheduled to complete the pre-participation testing. The participant and parent/guardian (if subject under the age of 18) will read and sign the “Consent to Participate in a Research Study” form, approved by the Institutional Review Board of Cincinnati Children’s Hospital. If the participant and parent/guardian does not read or sign the form, they will not participate in the study. Adult volunteers will be recruited via word of mouth or through affiliations with the teams/clubs noted above.

#### Inclusion criteria

- Enrolled in IRB study #2014-2946
- Normal female healthy volunteer (age
- Able to provide written consent

#### Exclusion criteria

- History of neurological deficits or severe head trauma
- Braces or permanent metal dental work
- Insulin pump
- Cardiac pacemaker
- Cochlear implants
- Hearing aids
- Aneurysm clips
- Orthopedic pins, wires, screws, or plates inserted within the last 6 months.
- If **not** enrolled in IRB Study #2014-2946

### **(7) PROCESS OF OBTAINING CONSENT**

Once a participant is identified as a potential participant, is contacted by a CCHMC/Sports Medicine representative and verbally agrees to participate, the process to obtain consent will begin. The study coordinator will review the informed consent and the participant will have an opportunity to ask any questions regarding the study and/or the study protocol. At that time, the participant 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 will be given a copy of the consent and testing will commence. At no time will the participant be coerced into participation. Receiving the informed consent prior to enrollment will allow the participants to review the study information prior to participation 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 the Parent Consent Form to obtain both the participant assent and the parent consent (if the subject is under the age of 18). The participants will be given adequate time to review the study materials and ask questions. If they choose to participate, the patient and parent will sign the IRB approved consent forms. It will be made clear to the patient and their parents that participation in the study is voluntary. Subjects over the age of 18 will complete the Adult Subject Consent Form.

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. The coordinator will ensure that all necessary forms have been signed prior to any data collection.

## **(8) STUDY PROCEDURES**

**Questionnaires:** A series of non-invasive questionnaires pertaining to general health history and knee pain will be administered. Specifically, the Anterior Knee Pain Scale (AKPS), shortened knee pain scale, the Tampa Scale Kinesiophobia questionnaire, the International Knee Documentation Committee (IKDC) scale, and a general demographics form related to age, sport participation history, etc.

### **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 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
- Any other exclusionary criteria as documented on the MRI safety screening poster included with recruitment materials those participants with any aforementioned contraindication will be excluded from study.

Testing will consist of two MRI sessions (approximately 6-8 weeks apart) using the 3T Ingenia scanners in the T-Building scanner and the 3T Acheiva scanner in the R-building at the CCHMC Imaging Research Center. 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 will 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 75 minutes or less.

## **(9) DATA ANALYSIS/METHODS:**

***Data Storage.***

The personal demographic data for each participant will be blinded from the researchers, and 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 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.

DTI data will first be subjected to preprocessing to correct for Eddy current and head motion artifact, followed by calculation of the three diffusion eigenvectors and eigenvalues. DTI measures, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) will be calculated. The regions of interest will be manually determined in major white matter areas such as corpus callosum, internal capsule, and external capsule. After being normalized to a common template, voxel based group analysis can be performed to explore brain regions that present significant group difference or longitudinal changes. Fiber tracking can be performed to generate white matter tracts in different areas in the brain, e.g., cortico-spinal tract, different segments in corpus callosum, optic radiation, cingulum superior longitudinal fasciculus, and others.

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.

**(10) FACILITIES AND PERFORMANCE SITES:**

All MRI scanning will be performed in the Imaging Research Center (IRC) in the Cincinnati Children's Hospital Research Foundation (CCHRf). Sedation will not be used for any of the test visits. The entire MRI series, including anatomical imaging, DTI, and fMRI, will be completed in 75 minutes or less.

**(11) POTENTIAL BENEFITS:**

Participants of this study will not receive any direct or immediate benefits by completing this study. However, they will be contributing to research involving the potential for major contributions to ACL injury prevention strategies.

**(12) POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:**

***MR Imaging of the Brain:*** The risk the magnetic fields and the strengths, and radio waves is vanishingly small. Some patients can experience anxiety from the confined space of the magnet's bore. Therefore people with known claustrophobic tendencies may be excluded from the study. 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 (who will be present and has a decade of experience with this technology) 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 in the IRC policy manual. The PI or Radiologist will notify the participant's primary care physician, participant or the participant's legal representative (or participant is 18 years or older) 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.*** As described in the consent, 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 director of social services who in turn will then contact CCHMC 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.

### **(13) RISK/BENEFIT ANALYSIS:**

Participants will be approached for participation via the appropriate method. The purpose and the study protocol will be fully explained in conversation and with the informed consent process.

On the day of the study, the investigators will confirm that the volunteer participant has no health impairment as outlined in the exclusion criteria. Time will be taken to repeat the aims of the study, test protocol, and to answer any remaining questions posed by the participant.

The methods described in this protocol have been used extensively in previous testing with our research team. During previous MRI/fMRI testing, there have been no reported injuries, adverse events or complications. Additionally, the investigators have considered potential risk for injury and have taken additional steps, described in the protocol, to minimize these risks.

#### **(14) DATA SAFETY & MONITORING:**

Dr. James Leach 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 (see Risk/Benefit Analysis section (15)). Further assurances regarding participant safety and protection of private and confidential participant information have been outlined in the Potential Risks, Discomforts, Inconveniences and Precautions section (14), the Privacy section (18) and the Confidentiality section (19). If during the, preliminary analyses the research team identifies strong evidence of harm from the Q-collar device the study will be stopped immediately.

#### **(15) PRIVACY AND CONFIDENTIALITY:**

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 CCHMC and have been trained in human participant's research and HIPAA compliance. To further insure 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. 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.

To further insure confidentiality, only pertinent research personnel will have access to participant information. Research personnel are employees of CCHMC and have been trained in human subjects research and HIPAA compliance.

**(16) COST OF PARTICIPATION:**

Participants will endure no costs other than time and effort in participating in this study. Insurance will not be billed for any of the tests associated with this study.

**(17) PAYMENT FOR PARTICIPATION:**

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. 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.

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