Neural Correlates of Knee Sensorimotor Control in Patients with Patelleofemoral Pain Syndrome.

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CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

STUDY TITLE: Neural Correlates of Knee Sensorimotor Control in Patients with Patelleofemoral Pain Syndrome.

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(1) ABSTRACT:

Patellofemoral pain (PFP) is a chronic condition characterized by retro- or peri-patellar pain during everyday activities that load the patellofemoral joint, such as sitting, jumping, or walking [1,2]. PFP is one of the most common knee conditions affecting the general population[3], affects approximately 1 out of 4 school aged youth[4,5] and is more common in females[6]. The pain associated with PFP adversely affects daily activities, reduces physical activity, and may contribute to patellofemoral osteoarthritis [7]. Participants with PFP exhibit aberrant biomechanics during functional movement[8-10] which we suspect may be, in part, due to altered brain activity in response to movement-associated pain. Participants with knee injuries do exhibit depressed sensorimotor brain activity in response to patella displacement relative to healthy controls[11], but these findings are limited as patella displacement is dissimilar to functional movement (e.g., flexing the knee and hip to get out of a chair). Our team, however, has successfully developed paradigms to assess knee motor control during functional movement (see methods below) using functional magnetic resonance imaging (fMRI) in healthy participants with no knee pain. We aim to replicate these paradigms in those with PFP to assess this populations' neurophysiologic response to knee movement. Results from this investigation will assist in refining subsequent training and prevention programs to promote more adaptive neuroplasticity.

(2) PURPOSE:

Our long-term goal is to alleviate symptoms of pain and reduce movement deficits for patients with PFP though innovative sensorimotor-targeted neuromuscular training programs. These programs will be designed to promote adaptive neuroplasticity, but an initial first step for this population is to determine the neural correlates of knee motor control in patients with PFP.

(3) BACKGROUND:

PFP is one of the most common reported knee conditions in adolescents and young adults[12,13]. PFP

can affect nearly 30% of young adults[14] and most frequently affect those who participate in athletic activities involving running, jumping, and cutting[5,13,15,16]. Pain during movement also adversely influences patellofemoral joint loading as evidenced by increased frontal and transverse plane hip motion during activities of daily living[8-10]. While the biomechanical and anatomical components contributing to knee pain have been well established, the underlying neural mechanisms are less understood. For adults with chronic pain (e.g., osteoarthritis), patients often exhibit greater 'pain network (e.g., anterior cingulate cortex, thalamus)' activation during sensory testing relative to healthy controls, possibly due to long term peripheral receptor activation resulting in hypersensitivity[17,18]. Further, inducing pain (e.g., pressing on a thumbnail) results in similar neural activation of the pain network for those who have chronic pain symptoms[19,20].

While these studies have been imperative to our understanding of pain on neural functioning, they are limited to those specific populations (e.g., fibromyalgia, osteoarthritis) and do not adequately replicate the pain experienced during daily activities. For example, patients with PFP often experience "movie-goer's knee" which refers to the pain experienced when keeping the knee flexed for long periods of time (such as sitting during a movie). Similarly, the condition has been referred to as 'runner's knee' or 'jumper's knee' as it is common in those who play sports and frequently place forces and stress on the patellofemoral ligament. Traditional approaches consisting of bracing and physical therapy focused on strengthening the knee extensors have been unsuccessful in reducing pain[21]. Further, interventions consisting of exercise therapy have not been effective for all patients with PFP[22-24], and other pain-reduction techniques, such as direct electrical stimulation of the motor cortex [25,26], have failed to produce improved motor function or long-lasting pain relief [27]. We hypothesize that this is due to the failure to appropriately challenge the full sensorimotor network involved in processing sensory and cognitive stimuli for motor control. To effectively treat pain and manage this condition, the neural correlates of pain and sensorimotor knee control in those with PFP is needed.

To our knowledge, only one study has utilized fMRI to assess brain activation for those with a history of knee injury[11]. Kadowaki et al.[11] had patients with medial patellofemoral ligament (MPFL) deficiency undergo fMRI while a researcher exerted a small amount of force to displace the patella during scanning. Results from their study revealed increased brain activation in areas associated with fear and pain and depressed sensorimotor brain activity relative to healthy controls. The authors concluded that the brain reorganized in response to the knee injury and is consistent with the framework that the brain undergoes neuroplastic effects in response to traumatic knee injuries[28,29]. The majority of previous investigations exploring pain and neural function, however, have examined brain function at rest, or utilized a pain inducing task dissimilar to everyday function (e.g., applying a piston to the thumbnail). To appropriately assess the pain network for those with PFP, replicating knee and hip motion *while* neural function is measured is needed. Our team has successfully developed a combined knee and hip extension and flexion task that can be used safely with fMRI at Cincinnati Children's Hospital Medical center. We have effectively collected data on multiple high school female athletes (with and without knee injuries) and aim to replicate and extend our findings to those with PFP. We hypothesize that those with PFP will display depressed

sensorimotor activity and increased pain network activity during our knee and hip flexion and extension task relative to our previously collected data.

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 our 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. Albeit the current proposal will investigate participants with knee pain (PFP), the tasks should induce no more pain than what these participants experience in day-to-day activities (e.g., getting up from a chair).

(4) STUDY DESIGN:

All MRI scanning will be performed on 3 Tesla Philips MRI scanners (3T Achieva in S-Building and 3T 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 lower extremity movements such as hip and knee flexion and extension. Also, for 15 minutes, the researcher will place one hand above the participants' knee and apply intermittent pressure to their quadriceps and medial aspect of the patella. VAS scales will be administered after every fMRI task to assess subjective perceptions of pain. 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.

The hardware and software are not FDA cleared, but also not FDA regulated as they are not medical devices. According to the FDA, a medical device is intended to diagnosis and or treat diseases while affecting the structure or function of any part of the body (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm). This is not the case for our study as our participants will already be diagnosed with PFP by a medical professional (we will not change this diagnosis) and our protocol will not alter any function or structure of the human body. Our leg press task is simply used to facilitate naturally occurring movement of the leg and hip and not intended to treat patellofemoral pain. Our method is simply to further our understanding of the neural mechanisms underlying natural movement in this population.

(5) DURATION:

Each participant will participate in 1 planned study visit that may take up to 3 hours. Data analysis will continue for a 2 year period following the final enrollment.

(6) SELECTION & RECRUITMENT OF PARTICIPANTS

We aim to recruit approximately 30 healthy female volunteers with PFP. Only females will be recruited for this study as they are 2 to 10 times more likely to develop PFP than males[30-32]. Females participants with PFP (age 7-40 years old) will be 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

- Normal female healthy volunteer aged 7-40
- Able to provide written consent
- Diagnosed with patellofemoral pain (PFP) or anterior knee pain by a medical professional

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 you have not been diagnosed with PFP by a medical professional

(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, a VAS pain scale, the Anterior Knee Pain Scale (AKPS), 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 1 MRI session using the 3T Ingenia scanner in the T-Building scanner 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 combined knee and hip flexion/extension movement and a quadriceps contraction task in which they will be asked to 'squeeze' their quadriceps while keeping the rest of their body still. For the last 15 minutes of MR acquisition, the researcher will place one hand above the participants' knee and apply intermittent pressure to their quadriceps and medial aspect of the patella. VAS scales will be administered after every fMRI task to assess subjective perceptions of pain. 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. The 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 future PFP intervention and 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 $100 Clincard Mastercard® gift card for completing the testing. 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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