

University of Minnesota

Functional Neuroimaging of Pain in Sickle Cell Disease

Study Protocol

Principal Investigator
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Oversight and Monitoring

The proposed human study is part of a program grant, which was reviewed by NIH study section. The study we propose to do at the University of Minnesota only involves noninvasive EEG and functional MRI to quantify pain.

The PI and Co-Investigators will monitor the safety of human subjects participating in the study. The research components only involve noninvasive EEG and functional MRI to quantify pain, which have been tested extensively in the PI's lab and in the field. The study procedures and status will be reviewed regularly and if any potential issue be identified, the study will be stopped, and a meeting involving the PI and Co-Investigators be called to review the situation and identify plan to address the issue. The study will be resumed if the meeting of investigators addresses the issue satisfactorily.

Overview of Study Design

Sickle Cell Disease (SCD) is an autosomal recessive disorder caused by substitution of a valine residue for glutamic acid at position 6 (or Adenine to Thymidine transversion on codon 6) in the beta-globin gene, resulting in sickle hemoglobin (HbS). Under low oxygen conditions, HbS polymerizes to form rigid fibers and confers a sickle shape to the red blood cells (RBCs). Sickle RBCs cluster together, occluding blood vessels and impairing oxygen supply to the limbs and organs, resulting in inflammation, oxidative stress, ischemia, end-organ damage and acute painful episodes called 'crises.' Hypoxia/reperfusion injury, inflammation and organ damage perhaps activates peripheral nociceptors.

SCD is associated with unpredictable recurrent acute pain episodes ('crises') and chronic pain that begins early in life. Opioid treatment remains a suboptimal approach due to side effects such as tolerance, addiction and altered renal clearance in SCD, resulting in morbidity and mortality. The lack of objective measures to quantify pain also contributes to inefficient analgesic therapy.

Our goal is to develop and evaluate a novel quantitative EEG (qEEG) technology for quantification of pain and imaging of brain networks involved in pain generation and processing from noninvasive dense array EEG. We will also develop a novel multimodal neuroimaging technology integrating fMRI and EEG for imaging of brain networks involved in pain generation and processing. We will test the hypothesis that qEEG can provide objective quantification of induced and spontaneous pain. We will test the hypothesis that the proposed qEEG and fMRI/EEG multimodal neuroimaging methods will be able to delineate and image brain networks involved in chronic pain and acute pain in SCD patients.

The proposed human study at the University of Minnesota involves only quantification of pain using noninvasive EEG and functional MRI. *No therapy component is involved in the human studies at the University of Minnesota.*

We will quantify and image induced pain and spontaneous pain. The induced pain study in healthy subjects has been already approved by the IRB (#1211M24481; PI: Bin He).

Quantification and imaging of spontaneous pain in sickle-cell disease patients:

We will directly investigate the pain severity assessment and brain pain imaging in SCD patients with spontaneous pain. Imaging spontaneous pain represents a challenge and the proposed study will be based on the novel techniques developed at the lab of Dr. Bin He.

Experimental protocol: We will study SCD patients and healthy control subjects using qEEG and fMRI (and structure MRI) recordings in a 3T MRI system. The SCD patients with different pain severity levels controlled by medication (as part of clinical routine) will be studied. SCD patients with chronic pain will be monitored using dense array EEG and fMRI. During acute crisis SCD patients will stay in hospital for 5-7 days as clinical routine, receiving infusion IV narcotics. EEG monitoring and fMRI monitoring (if feasible depending on patients' conditions) will be performed 30 min each to record acute pain due to crisis and chronic pain, when patients are under stable conditions. Within MRI scanner, the resting state recording will last for 6 minutes for fMRI recordings. The patients will be asked to have pain rating from score 0 to score 10 after each of the recording sessions. Control subjects will undergo 30 min EEG and fMRI recordings serving as baseline.

Data analysis will be performed offline to quantify the pain and correlate to patients pain ratings, and to image functional networks associated with pain generation. Statistical analysis will include comparing patient results to that of healthy controls in order to detect abnormalities within EEG and fMRI recordings. Group analysis will be performed with multiple comparisons correction. Additionally imaging results will be compared to pain parameters reported by patients and their physicians to detect if imaging results have any correlation to pain experienced by patients. Correlations will be defined at a p-value of 0.05 after multiple comparisons correction.

All subjects will be contacted for an introduction session for explaining of the study protocol, screening, and consenting. Subjects will be asked to give information on their neurologic diagnosis, the medications they are taking and any other health-related problems. The introduction session will last about 20 minutes.

Subjects will be asked to participate in either A) induced pain study or B) sponstenous pain study.

In study A, adult subjects with chronic pain or healthy subjects will be asked to sit quietly and comfortably, and recorded with EEG or lie down comfortably in a 3T MRI scanner recorded with fMRI. The session would last for about 1 hour.

In study B, adult or pediatric (ages 5-18 years old) subjects will be asked to sit quietly and comfortably, and recorded with EEG or lie down comfortably in a 3T MRI scanner recorded with fMRI. The EEG alone session will last for about 1 hour; the fMRI session will also last for about 1.5 hours. Subjects will be asked to relax. For SCD subjects with crisis, only those under stable conditions will be recruited to participate in the study of EEG and fMRI.

Prior to the fMRI session, subjects will be asked to complete additional safety screening form to ensure MRI safely. Subjects will be asked to pat down their body per CMRR safety guideline. Women subjects will be required to perform a pregnancy test prior to each experimental session. The proposed human study at the University of Minnesota does not involve treatment.

Subject Recruitment

Only patients at or above 5 years old are included as patients at or above this age will be able to complete the required resting state task. Patients will be assessed to see if they are able to perform the fMRI portion of the experiment. If the patient cannot perform in the fMRI experiment, then only EEG data will be collected.

Inclusion criteria:

1. 5-64 years of age
2. Patients with sickle cell disease at chronic stage or during crisis but under stable conditions

3. Healthy controls

Exclusion criteria:

1. Personal history of seizures or epilepsy
2. Previous surgical procedure to the spinal cord or brain lesion
3. Any metal objects or implantable devices, including but not limited to the following (dental metal is allowable):
 - Cardiac pacemaker
 - Implanted cardiac defibrillator
 - Carotid artery vascular clamp
 - Intravascular stents, filters, or coils
 - Aortic clip
 - Internal pacing wires
 - Vascular access port and/or catheter
 - Swan-Ganz catheter
 - Shunt (spinal or intraventricular)
 - Aneurysm clip(s)
 - Neurostimulator
 - Heart valve prosthesis
 - Any type of prosthesis (eye, penile, etc.)
 - Artificial limb or joint replacement
 - Bone growth/fusion stimulator
 - Bone/joint pin, screw, nail, wire, plate
 - Metal rods in bones
 - Harrington rods (spine)
 - Metal or wire mesh implants
 - Wire sutures or surgical staples
 - Insulin pump or infusion device
 - Any metal fragments (i.e. metal shop)
 - Any implant held in place by a magnet
 - Cochlear, otologic, or ear implant
4. Previous severe (i.e. followed by loss of consciousness) head or brain trauma.
5. Pregnancy
6. Breathing or movement disorder
7. Hearing aid use
8. Hearing problems or ringing in the ears
9. Metal in the brain/skull (e.g. splinters, fragments, clips, etc.)
10. History of traumatic, tumoral, infectious, or metabolic lesion of the brain, even without history of seizure
11. History of a fainting spell or syncope.
12. Claustrophobia
13. Non English Speakers
14. Blind or deaf that will make communication or task completion difficult/impossible.
15. Any other condition which would make the subject, in the opinion of the investigator, unsuitable for the study

Risks and Benefits

Risk of Collecting Personal Information:

The primary risk of collecting personal information is breach of confidentiality of such personal information about the subject.

Risks of MRI:

The risks of MRI include the potential dislodging of any indwelling metals (stents, joint implants that are not titanium, wire sutures, aneurysm clips, shrapnel, etc.), disrupting indwelling medical devices (cardiac pacemakers,

medication pumps, heart valve replacements, etc.), the risk of metal projectiles (coins, keys, hairpins, oxygen cylinders, etc.) inadvertently presented during the MRI scan, and the unknown effects of MRI on the unborn fetus. The noise inside the magnet is loud and can mildly disturb subject's hearing temporarily. Transient dizziness is sometimes reported by subjects upon removal from the magnet. Strong claustrophobia is a contraindication. In EEG/fMRI study, there is a risk for electrode heating, but we will use MR compatible devices (Brain Product), which has special design for use in an MRI scanner to avoid electrode heating.

Steps to Minimize Risks of Collecting Personal Information:

Subjects will be asked for only personal information relevant to the inclusion and exclusion criteria of the study. Only the principal investigators, co-investigators, and research associates/assistants/technicians working on the project will have access to identifying information. Subjects will be assigned numbers that will be used during all data analysis. The file containing study ID numbers and identifying information for all subjects in the study will be encrypted on a computer in a locked room. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes. Any information that is included in published manuscripts (e.g. area of brain lesion location) will not be linked to any other information that would identify the subject.

Steps to Minimize Risks of MRI:

In the screening process, we will ask subjects if they have any medical conditions or implants and if they are taking any medications. This is important to know so that only those subjects who meet the inclusion and exclusion criteria are accepted into the study. Subjects will also be screened for previous surgeries that might include noncompatible metal (nonferrous metals are compatible), indwelling medical devices, etc. Those who report having devices or noncompatible metals will be excluded. All female subjects will undergo a pregnancy test before each session, and females who are pregnant will be excluded from the study. Claustrophobia will be screened for in advance through interview. Subjects will wear earplugs and headphones during the MRI to protect against excessive noise. There is also a risk of heating or dislodgement of any metal objects. Therefore, subjects will be asked to remove all jewelry and piercings and female subjects will be encouraged not to wear an underwire bra during the scanning session. If the subject wears eyeglasses, they will take those off and will use non-metallic glasses matching their prescription, taken from a set of such glasses used by our laboratory for MRI studies.

At the completion of the MRI session, we will manage the potential dizziness in subjects by having them remain seated for one or two minutes and then walk them to the waiting area carefully. Subjects will not be dismissed until dizziness has subsided. In our experience, recovery from light-headedness has never taken more than just a few minutes.

If at any time during the MRI session, the subject experiences pain or discomfort, the testing will stop immediately. Furthermore, the researcher will observe the subject for any indications of further adverse events. Any adverse event will result in a temporary stop to the experiments while the activity is documented and further evaluated.

Potential Benefits

It is uncertain if there will be direct benefit to the subject for participation in the research, except for their knowledge that they are contributing to the establishment of an important noninvasive neuroimaging technology which may benefit other SCD patients in the future. The quantified pain information maybe helpful to the management of pain in the SCD patients.

Informed Consent Process

Consent will be discussed and obtained in an introductory session, before any tests have been scheduled. Subjects will be screened through an interview to ensure that they meet the necessary criteria. Consent will occur before any test data are collected or any treatment is given. For SCD patients, there will be waiting period between when their physician recruit them to the study to the formal consent process. For healthy subjects the consenting process will occur in the introduction session of the initial visit. A graduate student research assistant will be mainly responsible for explaining the experiment protocol and answer subjects' concerns. Subjects must provide their own consent. If

they are unable to, they will not be eligible to participate in the study. For minors under 18 years old, their parents or guardian will also need to give consent.

The prospective participant will be able to discontinue participation at any time. This component has been included in the pre-screening tool, the informed consent and the initial discussion. We are also asking those individuals who are contacted as potential participants to actively request more information therefore decreasing the likelihood of coercion.