# ClinicalTrials.gov Information

1. * **NCT Number:** NCT04723823

***The NCT number cannot be entered here until the study record is available on the ClinicalTrials.gov public site. This may take 2-3 days from when the NCT number is assigned to the record.***

2. * **Is the University of Pittsburgh or UPMC the Sponsor Organization for this study record?**
Yes No Clear
3. * **Who will be the Responsible Party for this study record?**

Principal Investigator of this IRB application

IND/IDE Sponsor, or another Principal Investigator (e.g., multi-center studies)

# Basic Study Information

1. * **Title of study:**
Mapping of motor and sensory brain activity using fMRI
2. * **Short title:**
Sensorimotor Imaging for Brain-Computer Interfaces
3. * **Brief description:**
We will use fMRI to map movement activity in motor and somatosensory cortex using enriched imagery in people with chronic tetraplegia. We expect that somatotopic organization of movement activity will be preserved in people with upper limb impairments, which we can quantify using the strength, area, and location of sensorimotor activity. Accurate mapping of the motor and somatosensory cortices using covert stimuli will help guide brain-computer interface (BCI) electrode design and placement. Moreover, these advanced mapping procedures will provide new insights into the functional interactions between sensory and motor areas of the brain after injury or disease.
4. * **What kind of study is this?**
Single-site study

# Study Aims

1. * **Describe the purpose, specific aims, or objectives and state the hypotheses to be tested:**
The purpose of this research study is to use functional magnetic resonance imaging (fMRI) to measure and locate brain activation relating to the movement, touch and position of various joints in the body to better understand the relationship between injury and function. Our goal is to optimize the sensorimotor brain mapping process to aid future studies for pre-surgical planning of brain-computer interface devices or to measure brain signal reorganization in individuals with upper limb impairment, or tetraplegia, due to a spinal cord injury or amyotrophic lateral sclerosis

(ALS).

Goal: Map sensorimotor cortical activity in people with tetraplegia using motor and sensory imagery. We will also obtain brain imaging of people healthy control participants with no neurological disorder and no impairment to be used for comparison.

We expect that we will observe the typical somatotopic organization of sensorimotor cortex, where hand-related activity is located laterally, with wrist, elbow, and shoulder being activated in progressively more proximal areas of motor cortex. The primary outcomes will be the strength, area, and location of peak activity for finger, wrist, and shoulder-related activity.

2. * **Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**

BACKGROUND: Advanced understanding of brain structure and function has improved the diagnosis and treatment of neurological disorders such as epilepsy, stroke, and spinal cord injury (SCI). Over half a century ago, the pioneering studies of Penfield used electrical stimulation of motor and sensory areas of cerebral cortex and revealed a distinct somatotopic organization of the brain. Today, this and additional knowledge of neuronal coding functions are being used to develop revolutionary devices that interface directly with motor and sensory neurons in the brain to establish functional connections with prosthetic and assistive devices. These so-called brain-computer interfaces (BCIs) require electrodes to be placed precisely in brain areas responsible for volitional control and sensation of limb movements, particularly the arm and hand regions. Mapping those brain regions is possible using functional magnetic resonance imaging (fMRI). However, such mapping studies are difficult to perform in persons with motor and sensory impairments. People with ALS and SCI have disrupted efferent and afferent pathways between the cortex and the limbs making it necessary to rely on covert techniques, such as kinesthetic motor imagery, to map sensorimotor brain activity in order to guide BCI electrode placement or to study cortical plasticity resulting from injury or intervention. Challenges associated with brain mapping after injury likely contribute to the widely varying reports regarding the extent and prevalence of functional reorganization occurring in the brain following SCI. fMRI is a non-invasive tool that allows for measurement of motor and sensory-related brain activity with minimal risk to study participants.

SIGNIFICANCE: Restoration of upper limb function is a top priority for individuals with tetraplegia. It is estimated that 236,000-327,000 people in the United States have a spinal cord injury. Approximately 17% of people with SCI have high tetraplegia (injury at cervical levels C1-C4) although this percentage has been increasing in recent years. People with high tetraplegia are the most likely group to benefit from BCI-controlled neuroprosthetics, although the covert mapping strategies developed in this proposal could be used to study sensorimotor activation and plasticity in anyone with motor or sensory impairment including amputation. Sophisticated, motorized prostheses are being developed that enable natural upper limb movement and have advanced sensing capabilities. We know that people with tetraplegia would like to restore function to their own limbs using FES, but this technology needs further advancement and does not replace sensation, which may still require a BCI. While FES research and development continues, people with tetraplegia could take advantage of motorized prostheses by mounting them to their wheelchair. Motorized prostheses can provide function comparable to that of an intact limb, but a high degree-of-freedom control interface is needed and BCI is one possible solution.

Functional neuroimaging can be used to guide BCI electrode placement in order to tap into existing sensorimotor circuits. Imagery-based brain mapping also enables the study of cortical plasticity which could be useful for understanding maladaptive cortical changes that occur after injury or beneficial changes resulting from rehabilitation interventions. Just as pre-surgical brain mapping may help identify individuals who are best suited for a BCI, covert brain mapping in

someone with motor and sensory impairments may inform the type of rehabilitation paradigm that is most likely to have a benefit. The potential benefit of being able to study cortical plasticity in the absence of movement or sensation is wide-reaching as it could be applied to patients with SCI, amputation, stroke, neurodegenerative diseases like amyotrophic lateral sclerosis, or other sensorimotor impairment. This specific study is being collected as a pilot investigation to establish pre-surgical planning procedures and we will collaborate with the University of Chicago who will conduct a similar pilot investigation to ensure consistency at both institutions.

## Study Design

1. **Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**
   15
2. **Describe and explain the study design:**
   Descriptive research classification, Observational methodological design
3. **Describe the primary and secondary study endpoints:**
   The primary outcomes of this study are the peak activity, location of peak activity and areas of sensorimotor and somatosensory brain activation.
4. **Provide a description of the following study timelines:**

   **Duration of an individual subject's active participation:**
   1-2 visits, up to approximately 4 hours
   **Duration anticipated to enroll all subjects:**
   3 years
   **Estimated date for the investigator to complete this study (complete primary analyses):**
   6/30/2022
5. **List the inclusion criteria:**
   1) Age 18 or older
   2) Normal or corrected to normal vision
   3) Impairment of at least one arm/hand as a result of cervical spinal cord injury or amyotrophic lateral sclerosis. The ALS diagnosis should be possible, probably, or definite ALS based on El Escorial criteria.
   4) Decreased or absent sensation or impaired hand movement
   5) Score of <10 on the Short Blessed Test cognitive assessment
6. **List the exclusion criteria:**
   1) Pacemaker, baclofen pump, cochlear implant or other electronic implanted device
   2) Metallic implant that is unsafe for 3T MRI
   3) Pregnant females
   4) Individuals who weigh over 300 pounds (because of MRI risks/space)
   5) Individuals who have difficulty breathing when laying down (orthopnea)
7. **Will children or any gender, racial or ethnic subgroups be explicitly excluded from participation?**
   **Yes** No

   * **Identify the subgroups and provide a justification:**
   We are focusing on adult subjects because we expect their brain activity to be fully mature and stable.

8. **Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):**
Up to fifteen subjects with upper limb impairment will be undergo fMRI testing at the University of Pittsburgh, and also, up to ten subjects will undergo fMRI testing at the University of Chicago (separate IRB at their institution). In addition to establishing a framework for a future collaborative intracortical BCI study, we will gather valuable information regarding the neural representation of hand movements and sensations using fMRI in up to twenty subjects with tetraplegia across both sites, which is an understudied area of neuroscience.

Peak activity, location of peak activity, and area of activation will be calculated for each condition from the cluster-analysis results. This is a pilot study so data will conducted on a single-subject level. We will qualitatively compare the results with previous data from our lab from able-bodied subjects and people with tetraplegia who have used implanted BCIs.

Collaborators at the University of Chicago will be collecting similar data. We may perform analysis of this data here at the University of Pittsburgh to verify consistency across two sites.

# Research Activities

1. * **Provide a detailed description of all research activities (including screening and follow-up procedures) that will be performed for the purpose of this research study. This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.**
SCREENING: MR safety screening: We will ask individuals if they have any implanted metal or electrical devices. If they indicate "yes" then we will ask them to provide written authorization for release of medical records to our research team in order to learn the specifics of their implanted devices (manufacturer, model, part numbers, type of metal, year of implant). Once this information is obtained, we will work with the manufacturer to provide details of any MR safety testing that was completed. If this cannot be obtained, we will consult with specialists who can advise whether or not an individual can be safely scanned. If necessary, we may also be advised about any special scanning instructions (such as taking longer breaks between individual scan paradigms). The MR safety screening inquiries may take place prior to study consent. After consent, a study participant will also undergo MR safety screening at the MRRC with an MR technician, using acquired supporting documentation.

Cognitive assessment: Cognitive function will be screened using the "Short Blessed Test." A sum total of <10 errors (out of a possible 28) is required for inclusion.

Medical record review: We will review a person's medical records, with their written authorization, to verify that they have a cervical spinal cord injury or ALS and that they will qualify for this study. This may occur prior to an in-person consent visit. After the phone screen, we may mail a completed authorization for request of medical records from their designated medical provider, together with a stamped envelope addressed to the research team, to the potential participant. They will be instructed to review this document, provide signature, and mail back to us. Once we receive this, we can verify that the person will qualify for participation in this study.

Pregnancy testing: Females of child-bearing potential will be given a pregnancy test prior to the scan. If found pregnant, the individual will not undergo MRI scanning and will be withdrawn from the study.

RESEARCH PROCEDURES: Subjects will undergo an MRI scan at the University of Pittsburgh Magnetic Resonance Research Center (MRRC). Other related procedures (questionnaires, function assessment) will take place at the MRRC consent room or lab space at the Rehabilitation and Neural Engineering Laboratories (RNEL). All procedures will be performed by the study team with possible assistance from the MRRC staff. Subjects will provide informed consent prior to participation in any of the experimental procedures.

QUESTIONNAIRES
Some subjects may be able to complete the questionnaire by placing a pen in their impaired hand or in their mouth, but typically, questionnaires will be completed by a research team member (researcher) and the study participant. The questionnaires are in paper form and these will be placed in sight of both the researcher and the participant. The researcher will explain the forms and ask the questions. The participant will provide their response, and the researcher will document their response on the paper forms. This does not require a participant to mark forms.

Basic DEMOGRAPHIC information including age, weight, height, gender, and ethnicity will be collected via questionnaire. Subjects will complete the Edinburgh HANDEDNESS Inventory. Subjects will complete the Kinesthetic and Visual Imagery Questionnaire (KVIQ-10), which quantifies motor imagery intensity and has been validated in people with disabilities. A PAIN Questionnaire will be used to quantify pain using a numerical rating scale (0-10) for hand, wrist, elbow, and shoulder pain. Subjects will also indicate locations of pain on a Pain Diagram using different symbols to distinguish types of pain (e.g. aching, stabbing, burning, numbness, and pins and needles). The questionnaires are expected to take approximately 15 minutes to complete.

FUNCTION ASSESSMENT
Motor and sensory abilities of the upper limb of individuals with spinal cord injury will be tested according to the ASIA International Standards for Neurological Classification of SCI (ISNCSCI) Exam Worksheet. Individuals with paralysis due to ALS will be assessed using manual muscle testing and/or the ALS functional rating scale (ALSFRS). A clinician or trained research staff member may assess upper and lower motor neuron function (e.g., through muscle strength and reflex testing) and spasticity using the Ashworth spasticity scale. The function examination is expected to take approximately 30 minutes. Manual muscle testing may be used to confirm that able-bodied controls have no impairment.

EMG / PRACTICE
Prior to undergoing the scan, subjects will be given an opportunity to practice the tasks that will be performed in the MRI. We may measure EMG activity during practice tasks before the MRI. Kinematics tracking, EMG measurements or sensory stimulation may be used during the practice session also.

MRI Dressing/Undressing
Participants will be told over the phone, prior to the testing date, how to dress for the MRI. Clothing should be comfortable, preferably made of natural fibers, with no (iron) metal (no zippers, snaps, jewelry, eyelets, etc.). They should arrive in the clothing that will be worn for the MRI. If any clothing changes need to be made, a private changing room is available at the MRRC, complete with available MRI-compatible clothes, if needed. A research team member (male or female, as preferred) can help in the dressing room, if requested and if a caregiver is not available. Also, lockers are available to store any valuables or clothing during the scan.

MRI
Structural MRI (3-D image of brain) will be performed to document brain anatomy. We will also collect functional MRI (fMRI) data while subjects perform different movements either overtly or covertly (i.e. through observation or imagery). If time permits, additional structural scans may be performed to assess white matter integrity. We may also use imagery or vibratory or tactile stimulation to evoke a sensory response. These stimulation devices may be attached to the skin with tape or adhesive. Sensory stimulation intensity will be adjusted so that it is not uncomfortable

or painful. The stimulation level is established with the participant's input, starting with an undetectable (or barely detectable) pulse. The pulse is incrementally increased until it is comfortably felt by the participant. Once this has been set to the participant's satisfaction, the MR scan including periodic stimulation pulses can begin. This process is repeated for each area of stimulation. Visual (e.g. video) or auditory stimuli may also be used to enrich the motor and sensory tasks. The duration of the scan may last up to 3 hours. This time can be split into multiple sessions and breaks may be taken, as needed. The participant will have a handheld alert squeeze-bulb to alert technician and the scan will be stopped immediately. If the participant is unable to use this squeeze-bulb, then a researcher will remain in the scan room near the participant so that verbal communication and visual monitoring can occur. In the event of an unanticipated finding during imaging, we will consult with a neuroradiologist and disclose this information to the volunteer and/or her/his physician should it require follow-up medical attention.

The following are examples of devices that would be used to deliver stimulation:

Vibratory: Dancer Design, Mini PTS type piezoelectric stimulators (http://www.dancerdesign.co.uk/products.html)

Tactile: Could be performed with a cotton swab, paintbrush, or by the experimenter touching or moving a subject’s finger (or other body part).

The research team will work with the MR Research Center to ensure that appropriate testing of stimulation devices related to MR safety has been completed.

The entire study visit is expected to take approximately 4 hours. The study may be split into multiple visits. If any data collected is deemed "inadequate" for any reason, we may invite a participant back to repeat that portion of the study.