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Microelectrode Brain-Machine Interface for Individuals With Tetraplegia

ClinicalTrials.gov #: **NCT01364480**

IRB #: STUDY19030235

FDA IDE #: G100298

IRB STUDY19030235 closure date: **11/26/2022**

FDA IDE G100298 study closure date: **11/22/2022**

- IRB approved STUDY19030235 consent form

University of Pittsburgh

School of Medicine
Department of Physical Medicine & Rehabilitation

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Microelectrode Brain-Machine Interface for Individuals with Tetraplegia

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SOURCE OF SUPPORT: Department of Physical Medicine and Rehabilitation

This research study is conducted under an Investigational Device Exemption (G100298) and is regulated by the Food and Drug Administration (FDA).

DESCRIPTION:

Individuals with tetraplegia (paralysis caused by illness or injury that results in partial or total loss of use of the arms and legs) have intact brain function but are unable to move due to injury or disease affecting the spinal cord, nerves or muscles. Brain-machine interface (BMI) technology is based on the finding that with intact brain function, neural (nerve) signals are generated even though they are not sent to the arms, hands and legs. By placing (implanting) electrodes onto the surface of the brain, individuals can be trained to send neural signals which are interpreted by a computer and translated to movement which can then be used to control a variety of devices or computer displays.

PURPOSE OF STUDY:

Figure 1. A NeuroPort Array and pedestal

The purpose of this research study is to demonstrate the safety and efficacy of using two NeuroPort Arrays (electrodes) for long-term recording of brain activity (neural signals). This study involves two surgical procedures approximately one year apart to implant and remove the NeuroPort Arrays. Both surgical procedures will be performed under general anesthesia. Two microelectrode arrays will be implanted in the area of the brain that controls your movements. The arrays are very small (4 mm x 4 mm, smaller than a pencil eraser) and are made up of 100 small electrodes that record brain activity (Figure 1). The array attaches to a connector that is fixed to the skull called a pedestal. Through this connector the electrodes send recordings of brain activity to a computer which will use the signals to control a variety of computer displays or external devices. External devices include things like computers or robotic devices that can potentially help you perform routine daily activities. Using neural activity to control an external device is referred to as a brain-machine interface (BMI) technology.

The NeuroPort Array is approved for recording brain activity up to 29 days by the Food and Drug Administration (FDA). We have received approval from the FDA to conduct a research study under an Investigational Device Exemption (IDE). As part of the IDE we will test the long-term safety and efficacy of implantation of the NeuroPort Arrays for approximately 1 year. We want to demonstrate successful control of virtual environments similar to computer games and assistive technology (things that can help you perform routine daily activities) including robotic, prosthetic limbs (mechanical devices that perform reaching movements or grasp objects) using a BMI operated by individuals with upper limb paralysis. Since placement of the device is temporary and part of a research investigation to determine the effectiveness of the NeuroPort Arrays, this study provides no direct benefit to you and participation is completely voluntary.

> Please refer to the description of the study procedures and risks that are included in this document. Also, the principal investigator and neurosurgeon will discuss these procedures and risks with you and answer any questions that you have.

We are inviting you to consider participating in this research because you have limited or no ability to use both hands due to cervical spinal cord injury (SCI), brainstem stroke, or spinal stroke. The limited strength in your hand must prevent you from being able to perform functional activities. You must be 18 to 70 years old. If you have a SCI or brainstem stroke, you must be at least one year post-injury. You must live within 1 hour of the University of Pittsburgh or be willing to travel to the University of Pittsburgh once per week for BMI training and expect to stay within 1 hour of or be willing to travel to the University of Pittsburgh for at least 18 months after enrollment. You must also have a caregiver, and a designated backup, who is able to perform necessary daily care of the skin and pedestal site. You must have a life expectancy greater than 12 months.

You cannot have a recent history of pressure sores. You cannot be included if you are unable to have a head MRI (due to certain metallic implants, a pacemaker or other devices). People who are allergic to contrast used for MRI or who have kidney problems are not eligible. Women who are pregnant or plan to become pregnant during the study cannot be included. Other exclusion factors include requiring routine MRI, therapeutic ultrasound or diathermy, osteomyelitis, active cancer within the past year, uncontrolled insulin dependent diabetes mellitus, history of seizures, autonomic dysreflexia within the last 3 months, severe skin disorders that cause excessive skin sloughing, lesions or scalp breakdown, a history of myocardial infarction, cardiac arrest, intractable cardiac arrhythmias or an implanted hydrocephalus shunt. We will not be recruiting Department of Defense (DOD) military or civilian personnel. You will have to meet other criteria to be eligible, which will be reviewed with you prior to your consent. We will screen ten people and expect that up to five individuals will complete this study.

STUDY PROCEDURES

As part of this study, you will complete the following procedures that will be conducted during multiple visits occurring over a period of up to 25 months. While it may be possible to schedule some of the procedures on the same day, you should plan to allow for a separate visit for each listed procedure. We will work with you to determine the testing schedule as early as possible.

Screening Procedures:

Procedures to determine if you are eligible to take part in a research study are called "screening procedures". For this research study, the screening procedures include:

- **Interview:** Once you contact our research team expressing an interest in the study, we contact you to review the study procedures, the risks involved, and the eligibility criteria during an initial screening either on the phone or in person. You will have an opportunity to ask questions and review the consent form. If we believe you are eligible, you will meet with the clinical and research team in-person for further discussion prior to enrollment. This interview will take place in research space at the University of Pittsburgh or UPMC. No research procedures will take place until you sign the consent form. After you agree to participate and sign the consent form, we will conduct additional screening. A physician-investigator or therapist will test the muscle strength in your arms. We may also visit your home to ensure that there is sufficient space for conducting research sessions. We expect the interview to take approximately 1 hour. In special cases we may need to access your medical records if additional information is required to assess your brain or spinal cord health and changes in functional ability.
- **Neuropsychological examination:** In order to test your intellectual functioning and mental health, you will undergo two standard examinations administered as questionnaires. You must meet a minimum level of functioning which will be determined by comparing your score to defined, acceptable scores, to be included. The psychologist will also conduct a brief interview to ensure that you have a stable support system. This examination is expected to take less than 30 minutes. This examination will be conducted by a neuropsychologist in research space at the University of Pittsburgh or UPMC.
- **Presurgical functional MRI (fMRI):** You will have an fMRI scan at the Magnetic Resonance Research Center at UPMC Presbyterian Hospital. fMRI uses a large magnet to take pictures of the blood flow in your brain while you do simple tasks such as imagining or attempting to move your hand or speak. The fMRI helps us identify the area of your brain that responds to imagined or attempted movement. This procedure helps determine where we will implant the electrodes. This test is expected to take less than 1 hour. You must be able to consistently activate a small area of the brain in order to be included. Women of childbearing age will be asked to undergo a urine pregnancy test as part of standard screening.

Experimental Procedures:

If you qualify to take part in this research study, you will undergo the experimental procedures listed below. Presurgical procedures and electrode implantation will occur within 6 months after the screening procedures are completed. Most of the procedures will take place on different days; however, we will work with you to determine the best testing schedule. You may be photographed or videotaped during any of the experimental procedures for research or educational purposes.

- **Questionnaire:** You will be asked to provide basic information about yourself (age, weight, height, etc.) as well as medical history information including the date of your injury or

diagnosis and current level of function. We will also ask questions related to your quality of life and BMI technology. The questionnaire should take less than 30 minutes. This questionnaire can be completed in research space at the University of Pittsburgh or UPMC or at your home.

- **Presurgical MEG (magnetoencephalography) scan:** MEG is a non-invasive tool that measures your brain activity. You will sit in a special chair while your head is positioned inside a helmet that contains sensors for measuring brain activity. During this test, we will ask you to imagine, observe, or attempt simple movements. We may also attach additional sensors to your head to measure head movement or eye movement or anywhere on your skin (most likely your arms) to measure muscle activity. We will repeat MEG testing after you have undergone BMI training to see if activity related to movement has changed (increased) due to BMI training. If you are unable or unwilling to participate in the MEG sessions, you will still be considered for this study. The presurgical MEG session is expected to take less than 2 hours. The MEG scan will take place at the UPMC Brain Mapping Center which is located at UPMC Presbyterian Hospital.
- **Presurgical brain-machine interface (BMI) training:** You may complete up to 5 sessions of BMI training using electroencephalography (EEG) and/or MEG prior to implantation of the electrodes. EEG records your brain activity using electrodes that are placed on your scalp. You will learn to use your brain activity to complete simple tasks such as controlling a computer cursor. If you are unable to successfully perform these tasks during presurgical BMI training, you may be withdrawn from the study or we may ask that you undergo additional training with EEG/MEG prior to implantation. The sessions will occur within one month and each training session will last less than 3 hours. The training will take place at the UPMC Brain Mapping Center which is located at UPMC Presbyterian Hospital, in research space at the University of Pittsburgh or UPMC or in your home.
- **Presurgical MRI (magnetic resonance imaging) scan and fMRI:** You will have a MRI scan either at the Magnetic Resonance Research Center or a clinical MRI facility at UPMC Presbyterian Hospital. MRI uses a large magnet to take a picture of your brain and skull structure. Both MRI and fMRI will be used with image guidance tools during the surgical procedures. You will have a contrast agent injected through an IV in order to improve the image quality. The MRI, including preparation time, will take less than 1 hour.
- **Pre-operative labs and screening:** You will undergo standard pre-surgical screening at the Anesthesia Pre-Op Clinic. The clinic staff will ask you about your medical history and perform a simple physical examination. You will be asked to provide a blood and urine sample. Less than 3 teaspoons of blood will be required for the sample. Standard lab tests will be run on these samples to ensure that you do not have risk factors that would make you an unsuitable candidate for surgery. Additional tests or treatments may be ordered at the discretion of the principal investigator or study neurosurgeon to assure your safety. Women of childbearing age will be required to undergo a urine pregnancy test. Sometimes the clinic requires an electrocardiogram (EKG), which is a test that places sensors on your chest in order to monitor your heart. They may also request a chest x-ray as part of this screening. If you have an active urinary tract infection, you will be required to pursue appropriate treatment (antibiotics) at your own cost prior to having surgery. Treatment for the urinary tract infection may be covered by your insurance. This visit is expected to last 1 hour and will be performed at UPMC Montefiore up to 30 days before your implantation surgery.

- **Surgical procedures:** The study neurosurgeon and surgical team will implant the NeuroPort Arrays which are each approximately 4 mm x 4 mm in size. The surgery will be performed at UPMC Presbyterian Hospital. You will be given antibiotics prior to surgery, as is standard protocol, to minimize the risk of infection. 1-2 grams of an antibiotic called cefazolin will be administered in the operating room through an IV. A different antibiotic may be used if you are allergic to cefazolin. You will be placed under general anesthesia for the surgery. A head holder will be used to keep your head still during the surgery. This will leave 3-4 small scabs away from the surgical site that should heal easily. Hair near the implantation site will be shaved to minimize the risk of infection. An incision will be made in the scalp to allow for implantation of the electrodes. A small bone flap (approximately 5 cm x 5 cm) will be removed over the motor cortex, which is the area of the brain identified in the presurgical fMRI screening. Additional mapping may be performed by a neurophysiologist to further verify positioning of the electrodes. The electrodes will be implanted using an inserter wand designed for controlled implantation. Each electrode will connect to a pedestal which is secured to the skull and will allow us to connect the electrodes to our BMI system. The two pedestals will pass through the scalp and will remain visible to others. The pedestals will be positioned so that they will not interfere with your comfort while you are lying down. Wires will be tunneled beneath the scalp to separate the electrodes from the pedestals. Each pedestal will be covered with a cap when the electrodes are not connected to our system. The bone flap will be replaced and secured with stitches or titanium or absorbable miniplates, which are small metal or absorbable strips commonly used in surgery. Impedance testing may also be conducted during surgery. This routine procedure involves applying a very small current to the array; no additional risks are expected. The entire surgical procedure is expected to last approximately 4-8 hours.
- **Post-operative hospital stay:** Post-operative care will depend on your condition, however we expect most participants will stay in the post anesthesia care unit for approximately 3 hours after surgery, followed by a 24 hour stay in the neurosurgical intensive care unit. You will then be transferred to the neurosurgical monitoring unit for 1-2 days (expected) to recover from surgery. All post-operative care will take place at UPMC Presbyterian Hospital. You will receive the normal standard of care for someone who has had electrodes implanted for clinical reasons, such as the treatment of epilepsy. This includes 23 hours or less of post-operative antibiotics. You will then stay at the UPMC Rehabilitation Institute for up to 10 days for post-operative rehabilitation. This provides an opportunity for you and your caregiver to become familiar with caring for the surgical sites while allowing medical staff to monitor wound healing. We may begin BMI training while the participants are staying at the UPMC Rehabilitation Institute. The study neurosurgeon and principal investigator will determine when you will be moved from each post-op unit. The principal investigator and rehabilitation team will determine when you will be discharged and allowed to go home.
- **Post-operative imaging:** You will have an x-ray and CT scan taken of your head within 48 hours after surgery to document the implantation site. This will be performed in UPMC facilities during your stay in the neurosurgical monitoring unit. If you experience severe headaches, nausea, and/or abnormal behavior you may need to have an additional CT scan. This will allow the neurosurgeon and clinical team to identify any possible infection or bleeding in order to treat them as early as possible.
- **Post-implant clinical evaluation:** A clinical investigator will perform monthly neurological

and physical examinations and perform wound checks. If changes are noted, appropriate medical care will be provided. These visits will likely be combined with research visits.

- **Brain-machine interface (BMI) testing:** Testing may begin as soon as you are recovered from the implantation surgery (expected 2-3 days following surgery). The electrodes will remain implanted for up to 1 year (+/- 30 days). During this time, we will conduct BMI training for up to 8 hours per day. Ideally we will conduct training for 5 days per week, but we will work with you to determine the best schedule. We may test everyday depending on what you decide with the research team. We will attempt to conduct at least 1 session per week. However, due to the long term commitment required by this study, we understand that scheduling conflicts may occur. There may be up to 6 weeks without testing sessions throughout the time of implantation (not necessarily consecutive weeks). We expect that training will be more frequent at the beginning of the study while you learn to operate the device and less frequent as the study progresses. Rest, meals, and other breaks will be scheduled as needed. Testing will normally take place in your home, however we may ask you to come to the University of Pittsburgh or a UPMC facility once per week for BMI training. During each training session, we will connect our BMI system to the pedestals attached to your skull. Our system records your brain activity measured with the electrodes and this can be used to control a computer cursor or an external device. There are two types of tasks that you will participate in:

    1) Open-loop tasks: You will be asked to respond verbally or with real or imagined movement to a simple stimulus, such as a visual or audio cue. We may record your movement during these tasks. The stimuli could be visual, audio, nerve stimulation using electrodes placed on the skin, or vibrotactile (vibration) feedback.
    2) Closed-loop tasks: You will learn to control your brain activity to generate a specified output. Examples of tasks range from basic, such as controlling a computer cursor or virtual hand, to advanced where you will learn to control an external device, such as a prosthetic limb or robotic arm.

  Impedance testing may also be conducted during BMI testing sessions to assess array function and tissue growth around the array. After each testing session, an investigator will remove and clean the cable which connects the electrodes to the computer. At a minimum, the pedestals should be cleaned every 7 days by a caregiver or study team member. We will provide detailed cleaning instructions to anyone who may assist with the cleaning. Cleaning supplies will be provided for home care.

  We will monitor your temperature once per day on the days that BMI testing occurs. You should monitor and record your own temperature every day. We can provide you with a calendar to record these measurements. Having a fever may be an early indicator of infection and will allow us to treat any problems early.

- **Counseling during implantation:** You will have opportunities to talk to a psychologist on the phone or in person throughout the study (approximately 1, 3, 6 and 9 months after implantation and prior to explantation) to give you an opportunity to discuss any concerns. The psychologist may refer you for additional meetings. In addition, physician-investigators, including the study PI and neurosurgeon, will be interacting with you on a regular basis and can refer you to a psychologist at their discretion. You may request meetings with the psychologist as needed while you are enrolled in the study.

- **Surgery to remove electrodes:** This surgery will be scheduled at UPMC Presbyterian Hospital approximately 1 year after the implantation surgery. It is possible that the electrodes may be removed earlier due to technical problems, clinical complications, or if either you or the investigators determine you should withdraw from the study. You may also be asked to give a blood sample (< 3 teaspoons) as part of standard pre-operative screening procedures. You will be given antibiotics prior to surgery, as is standard protocol, to minimize the risk of infection. Hair near the surgical site will be shaved to minimize the risk of infection. An incision will be made and the bone flap will be removed. Impedance testing may also be conducted during surgery. The study neurosurgeon will remove the electrodes and pedestals. The bone flap will be replaced and secured with titanium or absorbable miniplates. The scalp incisions will be closed with staples or stitches. You will be placed under general anesthesia for the duration of the surgery which is expected to take approximately 3 hours.
- **Post-operative hospital stay:** Post-operative care will depend on your condition, however we expect most participants will stay in the post anesthesia care unit for approximately 3 hours after surgery, followed by a 24 hour stay in the neurosurgical intensive care unit. You will then be transferred to the neurosurgical monitoring unit for 1-2 days (expected) to recover from surgery. All post-operative care will take place at UPMC Presbyterian Hospital. You will receive the normal standard of care for someone who has had a neural implant removed. This includes 23 hours or less of post-operative antibiotics. The clinical team will determine when you will be discharged and allowed to go home.

Monitoring/Follow-up Procedures:

Procedures performed to evaluate the effectiveness and safety of the experimental procedures are called “monitoring” or “follow-up” procedures. For this research study, the monitoring/follow-up procedures include:

- **Follow-up visit to monitor wound healing:** You will be asked to return for follow-up visits at the University of Pittsburgh or UPMC with the study neurosurgeon or clinical team at 1 and 4 weeks (+/- 3 days) after your surgery to remove the electrodes. They will check to ensure that the bone flap and pedestal sites are healing properly. Although unlikely, additional imaging studies (x-ray, MRI, CT) may be performed if the clinical team determines they are required for treatment.
- **Post-operative MEG (magnetoencephalography) scan:** We will ask you to return for up to three MEG sessions within 6 months after completion of the BMI training. The follow-up MEG sessions are optional. The MEG scans will take place at the UPMC Brain Mapping Center which is located at UPMC Presbyterian Hospital. If you are interested in participating, we plan to schedule these visits at 2 weeks, 6 weeks, and 3 months after the electrodes are removed. You will be asked to repeat the same tasks as you performed in the presurgical MEG session. Each visit is expected to take less than 2 hours.

  Please indicate if you are interested in participating in the optional MEG follow-up visits (You will be asked at the time of follow-up whether you are still interested in participating in the MEG scans. You may change your mind at any time and decide not to participate):

☐ YES ☐ NO

- **Counseling after device removal:** We will schedule an appointment for counseling with a rehabilitation psychologist after the device is removed to address any feelings of sadness that may be experienced.

RISKS and BENEFITS:

There are a number of possible risks, side effects, and discomforts associated with participation in this research study. As with any investigational study, there may be risks of adverse events or side effects that are currently unknown and it is possible that certain unknown risks could be serious, permanent, severe or life-threatening.

RISKS OF SURGICAL PROCEDURES AND CHRONIC NEURAL RECORDING

The most significant risks of this study are related to the surgical procedures performed under general anesthesia and chronic neural recording. You will undergo surgery twice within approximately 1 year as part of this study.

- **Surgical procedures conducted under general anesthesia carry additional risks that are specific to individuals with SCI.** Many individuals with SCI above spinal level T5 experience autonomic hyperreflexia, also called autonomic dysreflexia. This means that your blood pressure may rise in response to stimuli, such as surgical procedures. Since most of the surgical procedures will occur above the level of your injury, the risk of autonomic hyperreflexia during surgery is minimized. We will use a local anesthetic at the surgical site to minimize stimulation in this area. Hyperreflexia can also lead to a slowed heartbeat. Additional risks specific to SCI include an inability to regulate body temperature properly and respiratory compromise (trouble breathing normally). A neuroanesthesiologist experienced with procedures for individuals with disabilities will oversee anesthesia care for all study participants. We estimate these risks to be infrequent (1-10%).
- **General anesthesia for surgical procedures carries several risks (that are not specific to SCI) including some rare, but severe, risks.** Common, but minor and typically temporary, risks include nausea and vomiting (25%), sore throat (10-50%), post-operative pain (10-30%), headache (20%), drowsiness (50%), dizziness (20%), damage to the teeth or oral tissue (<1%), and peripheral nerve injuries (damage to nerves that link the brain and spinal cord to other parts of the body) (<0.3%). Serious risks, which are very rare, include vision loss or blurriness (0.0008%), hearing loss (0.1%), allergic reaction (0.01%), post-operative memory or concentration problems (1% for individuals over age 60), respiratory complications (0.03%), stroke (1%), and cardiac arrest (0.01%).
- **Antibiotics given in the operating room prior to surgery may cause side effects, although this is rare for a single dose.** The side effects include: fever, seizure, rash, itching, diarrhea/C. Difficile (a bacteria), nausea, vomiting, increased liver enzymes, and abnormal blood urea nitrogen or serum creatinine levels which are related to kidney function.
- **Neurosurgical procedures to implant electrodes carry several risks including some rare, but severe, risks.** Common, minor risks include mild to moderate headache, eyelid swelling,

bruising around the eye, minor swelling of the incision, and minor cerebrospinal fluid (CSF) leaks that are easily stopped. The risk estimates for more severe adverse events are based on electrode monitoring for epilepsy patients which typically use a much larger bone flap with the lead wires exiting through a hole in the scalp. Infrequent risks (occurring in 1-10% of people) that occur in this patient group are infection, bruising requiring additional surgery, bleeding requiring transfusion, CSF leak, and temporary neurological deficit. We will cover surgical sites with sterile dressing to reduce the risk of infection. There is also a risk of developing a pressure sore (skin and tissue damage that can be caused by pressure on the skin from staying in one position for too long) during surgery for individuals with SCI. Rare risks, that occur in less than 1% of people undergoing electrode monitoring include stroke, seizures requiring removal of the electrodes, or death. The bone flap may breakdown and not heal properly however this risk is rare (<1%). If this occurs, the study neurosurgeon may perform an additional surgical procedure to replace the bone flap with an artificial material

- **Chronic recording with NeuroPort Arrays: The major risks of chronic recording center around the long-term presence** of the NeuroPort Arrays and Patient Pedestals. The risks associated with the chronic implantation of the electrodes are expected to be similar to those observed with the implantation of other chronic devices such as deep brain stimulators and cochlear implants (implanted electronic hearing devices). These include but are not limited to thrombosis (blood clot), embolism (a blood clot that moves in the veins and can block blood from getting to vital organs like the lungs), body rejection phenomena (reaction by the body to the implanted array), neurological complications and infection. Infection is the most common complication for these types of devices, ranging from 4 to 12%. Based on our team's experience with other neurosurgical procedures, we expect the risk of infection to be less than 9%. If an infection cannot be treated with antibiotics, the electrodes may need to be removed. It is also possible that a participant who has limited ability to move their hand or upper limb may lose that ability due to implantation of the arrays. However, it is unlikely that local tissue damage resulting from the inflammatory response (body's immune response) will lead to functional deficits (impaired ability to perform activities of daily living). This risk is rare (<1%), as no such deficits have been reported in any of the previous animal or human studies.
    - Other common (>10%) risks include: bald spot, skin redness, fatigue, headache, incision site pain, nausea, ruptured blood vessels at pedestal site, scalp numbness, scarring, skin inflammation and irritation and tissue/capillary growth on healing wound surface.
    - Potential infrequent risks (1-10%) include: allergic reaction, blood clot near surgical site, loss of stability, dizziness, difficulty swallowing, tissue erosion (breakdown) around pedestal, temporary aggravation of underlying motor deficit, fever, hoarseness, high sensitivity to chlorhexidine (an antiseptic), tissue inflammation, neurological deficits, pedestal site pain or infection, psychiatric episodes, seizure, or wound healing difficulties.
    - Potential rare (<1%) risks include: adverse reaction to anesthesia, loss of ability to coordinate movement of neck and face muscles, attention deficit, rise in blood pressure, cognitive deficits, cramping, death, double vision, speech disturbance, brain inflammation, localized swelling in the brain, face or neck paralysis, brain hemorrhage, histotoxic reaction to implants (body's immune system treating implants as poisonous), immune rejection (body attacking implants), change in lead or sensor

position, meningitis, abnormal tonicity of neck muscle (increased or decreased muscle tension), neck pain, a non-healing wound, numbness, pedestal site drainage, bleeding during or after surgery, scalp tissue death, spasticity (muscle contraction), speech deficits, stroke, hematoma or paralysis of the vocal cord.

- **Excessive fibrosis (tissue growth) may prevent removal of the arrays.** There is a risk that it may not be possible to remove one or both of the arrays due to fibrosis (excessive tissue growth). This will be evaluated by the neurosurgeon during the explantation (removal surgery). If the neurosurgeon determines that the array(s) cannot be removed safely, the lead wires that connect the array to the pedestal will be cut and the pedestal(s) will be removed. The 4 x 4 mm array(s) would remain implanted. The risk of the array moving is minimal since the array would be encased in the fibrous tissue. If the array(s) remain implanted, you may not be able to have a head/neck MRI in the future. Alternative imaging techniques, such as CT scans, may need to be used however MRIs are more sensitive and accurate than other imaging modalities in detecting abnormalities such as malignancies. No additional follow-up visits are expected.
- **Array malfunction or failure**. If the array(s) fail due to technical issues which prevent the research team from recording brain activity, it will be recommended that you undergo surgery to remove the arrays and you will be withdrawn from the study. There will be follow-up visits with the study neurosurgeon to monitor your recovery.

OTHER STUDY-RELATED RISKS

- **Pre-operative blood work.** The insertion of the needle to draw blood may cause temporary discomfort, bruising from where the needle enters the vein, or soreness. There is a slight risk of infection. Fainting may occur, but this risk is expected to be rare.
- **EKG (heart monitoring).** There are no serious risks associated with EKG, however you may experience skin irritation after the sensors are removed from your chest.
- **MRI and fMRI scanning is associated with several risks.** There is the potential risk related to the machine itself attracting metal. Therefore, if you have metal within your body (e.g. aneurysm clips or pacemakers) you will be excluded from this study. Participants with dental fillings and most spinal fixators can be studied without risks. The magnet will make intermittent, loud, knocking noises that could cause ear discomfort in some people. Also, the rapidly switched magnetic fields used during imaging may cause nerve stimulation (e.g., an uncontrolled twitch or tickle near the waist). Because you must lie with your head and neck inside the narrow scanner tube, you may become anxious and frightened in the enclosed space. Some subjects will have suffered this reaction, called claustrophobia, in other situations. Should you develop claustrophobic feelings during the study, or for any reason feel that you cannot endure remaining in the scanner, the study can be interrupted and you will be able to rest outside of the enclosed area. You are in voice contact with the staff at all times during the MRI.
- **For the structural MRI, a contrast agent will be injected into your arm through a needle (small plastic tube). This carries additional risks.** The contrast agent contains a material called gadolinium. Injection of contrast may cause discomfort, tingling, or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% of people and go away quickly. There is a small risk of an

allergic reaction to gadolinium, although a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle to inject the gadolinium may cause minor pain, bruising, and/or infection at the injection site. People with severe kidney failure who receive gadolinium are at risk for developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD) (formation of excess connective tissue of skin, joints, eyes and internal organs that can create large areas of hardened skin). If you have kidney failure, you will be excluded from this study. Please notify the research staff, a doctor, nurse, or technician if you are allergic to gadolinium, if you have any kidney problems, or if you experience any side effects so that they can determine if you are at risk for developing NSF/NFD.

- **MEG testing has minimal risks** since it records brain activity non-invasively. We will incorporate rest breaks to minimize the risk of fatigue. There is a risk of developing a pressure sore, as with any activity that requires periods of sitting without changing position. We will use cushions and breaks for pressure relief activities to minimize this risk. As with the MRI, you may be at risk for feeling anxious or claustrophobic. You are in voice contact with the staff at all times.
- **X-rays and CT scans carry a risk of radiation exposure.** The maximum amount of radiation exposure you will receive from the x-ray is 0.3 rems (a unit of radiation exposure). You will have a head x-ray and possibly a chest x-ray completed as part of this study. The radiation exposure you will receive from the head CT is 2-5 rems. This is a fraction (12-28%) of the annual radiation exposure (20 rems) permitted to the most sensitive organs of radiation workers by federal regulations. There is no minimal level of radiation exposure that is recognized as being totally free of the risk causing genetic mutation (abnormal cells) or cancer. However, the amount of radiation exposure you receive in this study is considered to be low and comparable to everyday risks.
- **The tasks that we will ask you to perform during BMI training carry minimal risks.** You may be asked to attempt to control a prosthetic limb or robotic arm; however, these devices will, at first, be placed at a safe distance from you or a barrier will be used so that you are unable to physically interact with them. Once training familiarity with external devices such as a prosthetic limb or robotic arm is achieved, you may be allowed to physically interact with such devices in order to simulate daily living tasks. Doing so, there is a low risk (1-10%) of minor injury (bruising, scrapes) to you and/or your wheelchair by the robotic limb or dropped objects. Investigators will be present during all testing sessions to ensure safe operation of any external devices that are used. There are multiple levels of safety controls in place, incorporating both safety programming ("keep-out regions") and manual over-ride shut-off switching. We will adjust the difficulty of the tasks to minimize frustration and fatigue. You may experience skin irritation from the skin electrodes that we will use to record EMG (muscle) activity. We may stimulate nerves in your arm or leg which may cause discomfort or spasticity, but this testing can be stopped at any time. There is a risk of developing pressure sores during prolonged sitting. We will incorporate frequent rest breaks and encourage you to maintain your normal pressure relief activities. You may also experience frustration during BMI training, particularly early in the study. You will have opportunities to talk to a psychologist to discuss any concerns you are having. Additionally, investigators can refer you to a psychologist at any time throughout the study.
- **There is a risk of falling during transfers that are required as part of this study.** Some of the research activities, including the MRI, x-ray, CT scan, and MEG testing will require

you to transfer out of your wheelchair. Our staff will be available to assist you as needed and may spot you to ensure your safety.

- **Any task that requires prolonged sitting, or lying in one position, such as the MRI, CT scan, or MEG, carries the risk of developing a pressure sore.** We will encourage you to take frequent breaks to perform pressure relief activities and we will minimize the time required for the imaging studies.
- **You may feel let down or sad after the NeuroPort Arrays are removed and BMI training is over.** We will schedule an appointment for counseling with a rehabilitation psychologist to discuss these feelings.
- **Since personal information is collected, there is a risk of breach of confidentiality.** We will take the necessary steps to protect your information to the best of our ability. Research data will be collected using a coded ID to protect your private information. Contact information and other identifiable information will be stored separately. Photographs and videotapes will be stored digitally on our password-protected server. Hard copies may be stored in a locked file cabinet. At the end of this consent form is a space for you to give your permission (or deny permission) for pictures or videos that include images of your face to be used in research presentations or publications.
- **Women who are pregnant or plan to become pregnant during the duration of the study are excluded due to potential risks to the unborn fetus or themselves.** These risks include radiation exposure during x-ray or CT imaging which may lead to birth defects, mental impairment, cancer, or miscarriage. There are no known risks associated with undergoing an MRI scan while pregnant and the risks of MRI to the fetus are felt to be very small, but are nevertheless also not known. Any complications during surgery would put the fetus at risk for distress. We do not believe that pregnancy would carry any additional risks while the array is implanted, however this has not been studied and therefore the risks are unknown.

  Because participation in this study may harm a pregnancy, you must not become pregnant while you are in this study. If so, you must tell your doctor at once. If you are a woman and you are able to become pregnant, you will have a urine test to make sure that you are not pregnant before you are permitted to undergo the experimental procedures. If you have questions, you are encouraged to speak with either the study doctor or your personal physician.

BENEFITS:

You will not receive any direct benefit from taking part in this research study. This study involves long-term placement of two electrodes for BMI testing. This study will provide the basis for long-term BMI development with a high degree of user control and may benefit people with tetraplegia in the future.

NEW INFORMATION:

If we learn of any new information about study risks that could cause you to change your mind about continuing to participate we will notify you promptly.

COST AND PAYMENTS:

Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above). If you get a bill or believe your health insurance has been billed for something that is part of the study, notify a member of the research team. Any procedures performed for routine medical care will still be billed to you or your insurance company; you will be responsible for any co-payments.

You will be compensated for participating in this research study. You will participate in up to 10 study visits (neuropsychological examination, fMRI, pre-surgical MEG, pre-surgical BMI training sessions, MRI, and pre-operative labs) prior to the implantation surgery for which you will be compensated $50 for each visit or day of testing that you complete. The maximum compensation prior to the implantation surgery is $500.

We expect that the implantation surgery and post-surgical hospital and rehabilitation stays will last up to 13 days and you will be compensated $50 for each day you spend in the hospital. This is a maximum of $650, even if the stay lasts longer than 13 days.

You will participate in BMI training while the NeuroPort Arrays are implanted. You will be compensated $200 per month for your participation. For 12 months of participation, this is a maximum of $2400. If you are withdrawn by the investigators due to an adverse event or technical problem, you will be compensated for this entire amount regardless of how long the NeuroPort Arrays are implanted.

We expect that the NeuroPort Array removal surgery and post-surgical hospital and rehabilitation stays will last up to 6 days and you will be compensated $50 for each day you spend in the hospital. This is a maximum of $300, even if the stay lasts longer than 6 days. You will participate in up to 5 study visits (clinical follow-up visits and follow-up MEG testing) after the NeuroPort Arrays are removed for which you will be compensated $50 for each visit or day of testing that you complete. The maximum compensation after the removal surgery is $250.

The maximum amount of compensation for this study is $4100. You will also be reimbursed for mileage costs at the standard IRS rate since you will be required to drive to UPMC or the University of Pittsburgh for some study procedures. You will be provided with validated parking tickets for UPMC parking garages for study visits. If you withdraw from the study, you will be compensated for all completed study visits at the rates described above. Please contact a research team member if you have questions about payment.

COMPENSATION FOR INJURY:

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will

be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

CONFIDENTIALITY:

Any information about you obtained from this research will be kept as confidential (private) as possible. All paper records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a coded ID rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. Imaging studies (such as MRI, fMRI, or x-ray), photographs, and videotapes will also be stored electronically using your case number on our password-protected server. Any hard copies will be stored in a locked file cabinet with the rest of the research data. All electronic records will be stored on a password-protected server.

This research study will result in identifiable information that will be placed into your medical records held at UPMC Presbyterian. The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record includes any imaging study results (MRI, x-ray, CT, MEG) or surgical procedures. The staff at the MRI and MEG research centers will have access to your identifiable information related to the scanning procedures. Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., physician office) records. The information that will be recorded will be limited to information concerning any changes to your brain or spinal cord health or changes in your functional ability. This information will be used for the purpose of assessing potential changes related to training or other study procedures. In special cases, investigators may access previous medical records to assess your ability to participate in this study.

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office, as well as a Data Safety and Monitoring Board, may review your identifiable information for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information related to your participation in this research study **in response to an order from a court of law**. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the U.S. Food and Drug Administration may review and/or obtain identifiable information related to your participation in this research study for the

purpose of monitoring the accuracy of the research data. While the U.S. Food and Drug Administration understands the importance of maintaining the confidentiality of your identifiable research and medical information, the University of Pittsburgh and UPMC cannot guarantee the confidentiality of this information after it has been obtained by the U.S. Food and Drug Administration.

Authorized representatives from the Department of the Navy Human Research Protection Program may review and/or obtain identifiable information related to your participation in this research study as part of their responsibility to protect human research subject volunteers.

We may share your de-identified research information with other researchers interested in this topic at the University of Pittsburgh and other centers.

Your information will be maintained by the investigators after your participation is completed. The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of seven years after final reporting or publication of a project.

You may access medical information that results from participation in this study. In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information contained within your medical records filed with your health care provider.

RIGHT TO PARTICIPATE or WITHDRAW FROM PARTICIPATION:

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above. **If the investigators feel that you cannot complete the study requirements safely, they may withdraw you from the study.**

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If you decide to withdraw from the study, you may be asked to continue some research procedures to maintain your safety. If you decide to withdraw from the study while the NeuroPort Arrays are implanted, we will schedule a surgery to remove the electrodes as soon as is possible. You will still be required to return for the follow-up visit with the study neurosurgeon 1 and 4 weeks after surgery to observe wound healing. No other follow-up procedures will be required unless dictated by your medical condition. If you withdraw before the electrodes are implanted, no additional follow-up is required. If you withdraw after the electrodes are removed, you will be required to return for the follow-up visit with the study neurosurgeon, but you are not required to return for MEG testing.

If you experience an adverse event or complication resulting from serious non-compliance then you will be financially responsible any necessary medical care. Serious non-compliance is defined as not completing essential study visits including the surgery to remove the electrodes and the post-operative hospital stays. By not completing these procedures as specified in the protocol, you may increase your risk of complications.

Removal of the Arrays

If the study team recommends removing the NeuroPort Arrays for your safety and you do not wish to have the NeuroPort Arrays removed, you may be placing yourself at an increased risk for complications. BMI training will not continue if you do not comply with the study team's recommendation. Further, **you will be financially responsible** for any medical care that is needed after you are withdrawn as recommended by the principal investigator. However if you choose to have the device removed at any time the clinical costs will be covered by this study. In order to avoid this situation, please acknowledge that you will agree to comply with requests from the principal investigator to remove the device by initialing below.

Participant's Initials: _____

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VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____	_____	_____
Participant's Signature	Printed Name of Participant	Date

By participating in this study, I understand that I will be photographed, videotaped or recorded. These pictures, videos or voice recordings may be used for research or educational purposes. Pictures, videos or voice recordings will not be used for potential media stories until I sign a separate consent form. By <u>initialing</u> below,

_____ I give my permission to use photographs, videos or recordings that contain images of my face or recordings of my voice for research or educational purposes.

_____ I do not give my permission to use photographs, videos or recordings that contain images of my face or recordings of my voice for research or educational purposes. I understand that I will still be photographed, videotaped and/or recorded as part of this study.

VERBAL CONSENT

_____
Participant's Name (Print)

This participant provided verbal consent because they are unable to sign. I have witnessed this participant's verbal consent.

_____	_____	_____
Witness's Signature	Printed Name of Witness	Date

FAMILY MEMBER/PRIMARY CAREGIVER CONSENT
I acknowledge my role of primary caregiver. I understand the requirements of participation and agree to support the participant in this study.

_____	_____	_____
Caregiver's Signature	Printed Name of Caregiver	Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study
_____	_____
Signature of Person Obtaining Consent	Date