Title: Virtual Neuroprosthesis: Restoring a Sense of Touch to Amputees

Clinical Trials number: NCT03581448

Protocol and Statistical Analysis

August 18, 2021

SCH: INT: Virtual Neuroprosthesis: Restoring Autonomy to People Suffering from Neurotrauma

1. Project Summary: The goal of this project is to quantify motor task performance (tasks reminiscent of everyday life such as object transportation, arm motion and reaching) in normal subjects, amputees and limb-absent people controlling a robotic arm and hand. Participants are subjected to a virtual loss and recovery of their tactile experience via modulation of a noninvasive haptic feedback system attached to their body, to mimic the experience of neural plasticity that occurs during peripheral nerve regeneration. We hypothesize that trials during which subjects are provided with more accurate, less noisy haptic feedback will lead to stronger and more timely somatosensory activity as measured with EEG neuromarkers, which in turn, will lead to better behavioral performance while using the artificial hand. This research plan is minimally intrusive to people and poses only minimal risks commonly encountered in daily activities.

2. Objectives: Our specific aim is to determine the optimum conditions that promote sensory restoration in limb-absent people, with the development of adaptive haptic feedback laws and protocols that mimics the experience of neural plasticity.

3. Background & Rationale: Toward developing haptic-smart limb prosthesis: One significant challenge for people who use prosthetic hands is the inability to directly feel anything that is grasped by the prosthesis (grant proposal sections 1.2-3 for detailed rationale and references). An invasive method at the cutting edge to reconnect limb-absent subjects' sense of touch is through direct neural feedback with an implanted electrical stimulator in the nervous system (grant proposal section 1.5). This has been helpful to reconnect a severed sense of touch with sensors on their prosthetic hands (grant proposal section 1). But the self-organizing process of peripheral nerve pathway restoration, which is well studied at the physiological level *in vivo*, is complex and more poorly understood at the functional level (grant proposal sections 1.4, 2.3, 2.5). To develop restoration of haptic sensation in users of prosthetic hands, two important questions need more research: how does the functional process of sensory restoration occur in people with damaged peripheral nerves undergoing regeneration? And to what extend does somatosensory restoration depend on the action of the person and its corollary pattern of afferent action potentials? Answers to those questions are progressing slowly with invasive studies, due to restrictions placed on safety and ethics while experimenting with electrode implantation and nerve stimulation *in vivo*. Our proposed virtual neuroprosthesis circumvents those limitations by setting a surrogate regenerating nerve *in vitro*. Rats' peripheral neurons are cultured in microfluidic chambers and then subjected to trauma. By participating in experiments in which they control robotic arms and hands, subjects contribute to the regeneration of the traumatized neurons *in vitro*: the haptic experience that their actions causes is sensed by the robotic hand and transformed into biologically-realistic trains of action potentials, which are conveyed to the cultured nerves to stimulate nerve regrowth electrotactically. In return, impedimetric and microscopic assessments of nerve regeneration are used to modulate the quality of an indirect haptic feedback received by the subject (a pressure-varying cuff actuator applied to a proximal limb site), so that interaction between action and perception can be studied in humans while *in-vitro* neurons regenerate. Subjects are never in direct contact with the nerve culture in any way (the state of cultured nerve regeneration just becomes a control parameter to modulate how clearly haptic feedback is provided to the subject, with poorly regenerating nerves giving rise to poor haptic feedback and vice versa), and the haptic stimulation is entirely noninvasive, making this experimental program one with minimal risks. From the viewpoint of the subject, the experiment just looks like a psychophysics study during which tactile information is varyingly facilitated or impeded during task performance.

4. Research Plan:

(a) **Study Design and Timeframe of the Study**

The study follows an experimental research plan under consideration for an award at NIH and its performance is planned for a duration of 4 years. All experiments are conducted on the Boca Raton Campus of Florida Atlantic University. The study includes a fractional factorial experimental design with repeated measurements.

(b) **Research Methods**

Over one or multiple days, we examine neurobehavioral processes in people controlling a robotic arm and hand to perform simple motor tasks (e.g. fragile object transportation), while a virtual peripheral nerve regeneration protocol provides users

with biologically-realistic, idiosyncratic parameters for the restoration of haptic sensation (in double-blind fashion, the cellular neurophysiologists characterizing neural regeneration with microscopy are unaware of subjects' name and condition; and the human-subject experimenters are unaware of the haptic feedback parameter that will be used in the experiment each day, which is entered by the neurophysiologist in a black-box section of the software in the case of microscopic evaluation of nerve regeneration (early part of the project), or which is automatically input by the system in the case of real time impedimetric measurements (later part of the project)). The main experimental factors are 'haptic feedback', with three modalities: full, partial (nerve-regeneration dependent) and null; and to challenge human control strategy and impose demand on haptic information, the 'transported object weight' (heavy, medium and lightweight).

Recording techniques: Subjects' electroencephalography (EEG), electromyography (EMG) and behavioral performance scores (number of drop and breakage, speed) are recorded, as well as subjective self-report (perceived task difficulty).

Other significant materials: Subjects are equipped with a soft haptic feedback armband, a cuff with variable inflation that informs of the pressure measured within the robotic hand as it manipulates objects. Subjects face a computer display (initial training session) or the robotic arm and hand (subsequent sessions).

Procedures: After explanation of the experimental goal and signature of a written informed consent, subjects are prepared for EEG recording, an EMG array and a soft haptic feedback armband are placed on their missing (or dominant) hand. In a series of trials, they use a robotic arm and hand to perform a fragile object transportation task or various control motor actions. The task parameters are varied between trials (presence and quality of haptic feedback, weight of the visually-identical object). The task, including EEG, EMG and armband preparation, instruction and numerous breaks, and removal of the EEG electrode array, is under 2 hours. No activity is physically strenuous and subjects can ask for a break at any time. While in preliminary phases of this study, we may need to test one of more of these individual subsystems (EEG, EMG, soft actuators) independently with human subjects. Thus on the consent form we have specified this by including boxes to be checked for the combination of EEG, EMG, and soft actuators that will be evaluated during experiments.

Time commitment: Each experiment will last at most 2 hours. Subjects are free to withdraw from the study at any time with no repercussion whatsoever. At the end of each experiment, subjects are offered continued participation over the consecutive days of the week.

(c) **Study Population**: Subjects are 18-65y.o. volunteer with intact limbs, amputation or congenital limb absence. Inclusion criteria are normal/corrected-to-normal vision, general good health. Exclusion criteria are an amputation wound that has not yet healed, the absence of a suitable length of residual limb for placement of haptic feedback controller and EMG sensors, presence of pain that prevents utilization of those experimental appliances and the use of psychoactive drugs that modifies baseline neural activity.

Dr Engeberg has demonstrated the ability to recruit amputee subjects and successfully design robotic control experiments for them (grant proposal section 2.1-2 and 3.6). Based on a power analysis of preliminary data of grasp performance metrics with amputees and best estimates (standardized probability of 0.05 and statistical power of 0.8), a minimum of seven subjects will be required for adequately powered behavioral analysis. EEG analysis, on its side, requires a minimum of 12 subjects per group (Picton et al., Psychophysiology, 2000). Therefore, our study aims for 3 x 12 subjects (control, amputees, limb absent) and provides for pilot data collection and expected attrition to a total of 50 subjects. (Past experience has shown amputees and limb-absent people to be dedicated experimental volunteers, therefore at the present time, we factored an attrition rate of 32%.

d) **Recruitment Plan:** We plan to recruit test subjects by distributing flyers throughout Florida Atlantic University campus which describe the key points of the experiment and lists Dr Engeberg's office phone number and email address. Due to the difficulty in recruiting well-qualified limb-absent subjects, flyers may also be posted on campuses of nearby universities, including Florida International University, Nova, etc.

After volunteers contact the experimenters, we will screen subjects for inclusion/exclusion criteria over the phone and for those included, we will arrange a time to perform the first experiment. Before the experiment, we will explain the study objectives and procedures, answer questions and then we will ask subjects to read and sign the informed consent form.

A participation stipend will be offered to the participants in the studies in the form of prepaid gift cards from Amazon or equivalent, with no penalty if the subject withdraws during the session. We propose to compensate all subjects who participate in this study with $80 to offset their travel time and expenses.

(e) **Analysis Plan:** We compare the neural (somatosensory neuromarkers) and behavioral characteristics (performance, subjective report) for each object weight and each feedback modality. We hypothesize that trials provided with less noisy, more accurate tactile feedback will lead to stronger and more timely somatosensory activity as measured with EEG neuromarkers, which in turn, will lead to faster and better behavioral performance while using the artificial hand. EEG analysis is conducted using the methods developed by Tognoli et al., PNAS, 2007. Nonparametric Mann-Whitney U-tests will be performed on the subjective evaluations and a multifactor ANOVA will be performed on the quantitative success rates related to the number of times the objects were dropped or broken, and the speed of transport. Results will be disseminated as oral and poster presentations at conference, proceedings and journal submissions.

5. Benefits: This study presents minimal risks and offers no direct health benefits to the participating subjects but aims to advance understanding on the behavioral and brain mechanisms underlying somatosensation and its plasticity. Participation in this experiment is important for society. Increased understanding on the plasticity of somatosensation will be broadly useful for behavioral neuroscience. The scientific advances expected to result from this research will specifically benefit amputees and limb-absent people who use prosthetic hands or disabled individuals who rely on robotic assistants. There are others who could benefit from this research as well, for example, doctors who perform robot-assisted surgery and their patients, or people having suffered from neurotrauma.

6. Risks: This study will involve no more risk than encountered during routine medical, psychological examination or during daily life. The EEG employed in this study is a medical grade system with optical isolation that prevents electrical risk. Sensitive EEG equipment is single-use and sterile (syringes, canula, qtips), or when not possible (EEG and EMG electrodes), decontaminated with compliant medical procedures for infectious risk. All personnel participating in this research are trained and certified by Dr Emmanuelle Tognoli, who has managed EEG training at the Center for Complex Systems and Brain Sciences since 2004.

Application of EEG and EMG electrodes presents a small risk of skin irritation that is rare and usually disappears within a day or two. Application of the haptic stimulator is calibrated to avoid excess pressure and pain, and subjects are encouraged by instruction to provide continuous feedback on discomfort.

Performance of the robotic control task is designed to minimize strain and fatigue. There are small risks of tension or fatigue in the muscles of the limb used to generate the robotic control signal; of visual fatigue while concentrating on the computer screen or robotic hand; of important demand on attention leading to mental fatigue. Those effects are rare and, based on previous studies, we expect that no adverse consequence persists beyond a few hours. Experimenters are present at the side of the subject at all time, and subjects are free to interrupt a session at any time.

7. Informed Consent Process: After volunteers contact the experimenters by phone or in person, we will ask subjects for verbal consent to conduct the screening for inclusion/exclusion criteria. We will inform subjects that they are free to answer each and all questions from the screening procedure. Upon acceptance, the experimenter will then go through the screening procedure, and for people meeting the inclusion requirements, will arrange a scheduled time to perform the first experiment. Just before the scheduled experiment, we will explain the study objectives and procedures, answer questions and then we will ask subjects to read and sign the informed consent form.

(a) Inclusion/ exclusion screening procedures: Subjects are asked details about their vision (normal/corrected-to-normal; poor; Prefer not to answer [PNTA thereafter]), general good health (yes, no, PNTA), if appropriate amputation type, healing status (yes, no, PNTA), presence of neuropathic pain (yes, no, PNTA), and use of psychoactive drugs (yes, no, PNTA).

(b) Deception: No deception will be used either during the screening process or during the experiment.

(c) Cognitively- or decisionally- impaired subjects: We will not enroll cognitively or decisionally-impaired subjects. Some subjects will have a physical disability (absence or loss of a limb): such does not affect their ability

to understand the purpose and procedure of the experiment, or to make an informed decision to participate and provide informed consent.

(d) Emancipated minors: We will not enroll emancipated minors.

(e) Non-English speaking subjects: We will not enroll non-english speaking subjects.

8. Informed consent document: Human subjects will be informed of the study objectives and procedures before being proposed to consent to participate. We will indicate that participation is on a voluntary basis and we will use a written informed consent, approved by FAU IRB and current, to document voluntary participation.

9. Research Materials, Records, and Privacy:

(a) type of information collected: We will collect demographic information as required by NIH enrollment report if consented by the subject (subjects are able to decline each and all questions), in an anonymized, cumulative data table. In anonymized digital and paper data records, we will collect behavioral data (time series reflecting the activity of body parts), EEG/EMG data. Data is acquired by an EEG/EMG/robotic computer system and custom-made computer programs.

(b) storage of research information: Anonymized data (random code identifier) will be encrypted and stored in a password protected computer in the laboratory of Dr Engeberg, and copied on password-protected digital media. Consents will be stored in a locked file cabinet in the laboratory of Dr Engeberg and the key will be available in the principal investigator's office. Anonymized data will be accessed by the investigators listed on the IRB application. We will destroy the informed consents after a period of 4 years, but we will aim to preserve the anonymized data so that it can be further re-used by ourselves, collaborators and other scientists making request of them. We expect this study to be supported by NIH or NSF (grant submitted under a joint panel). NIH, as well as other agencies, have articulated a strong inclination for the preservation of taxpayer-funded scientific data (Collins & Tabak, Nature, 2014; Federer et al., PLOS One 2015). NSF has the following policy: *"Investigators are expected to share with other researchers, at no more than incremental cost and within a reasonable time, the primary data, samples, physical collections and other supporting materials created or gathered in the course of work under NSF grants. Grantees are expected to encourage and facilitate such sharing."* (https://www.nsf.gov/bfa/dias/policy/dmp.jsp). It is also customary in our field that data is preserved for replications and confirmation studies, and several target publications for our research require that we accept requests for data sharing from other scientists.

10. Resources:

(a) Resources/facilities at FAU: Personnel involved in the data collection are Faculty at FAU, Drs Engeberg and Tognoli, FAU students, and subjected to amendments of this IRB, to-be-hired postdoctoral fellows and research assistants. All have received a training for EEG recording and safety. Recordings will take place in the laboratory of Dr Engeberg, Engineering West.

(b) Resources from other sites: No research activities involving human subjects will be conducted at performance sites that are not owned or operated by FAU.