Mass General Brigham
Mass General Research Institute

Official Study Title	Effects of Transcranial Electrical Stimulation on Task Performance in Healthy Adults
ClinicalTrials.gov Identifier (NCT)	NCT06995560
Study Sponsor	Massachusetts General Hospital
Principal Investigator	Gary E. Strangman, PhD
Affiliation	Massachusetts General Hospital / Harvard Medical School
Study Type	Interventional Study
Intervention	Transcranial Electrical Stimulation (tES)
Primary Outcomes	ROBoT-r Task Performance (During and Post-Stimulation)
Secondary Outcomes	tES Adverse Effects Questionnaire; fNIRS Hemodynamic Activation (HbD)
Document Type	Study Protocol
Protocol Date	April 4, 2024

Protocol Title: Preliminary investigations of transcranial electrical stimulation effects on neurophysiology and behavior

Principal/Overall Investigator: Gary Strangman, PhD

Description of Subject Population: Healthy, adult volunteers, age 18-64

I. BACKGROUND AND SIGNIFICANCE

Transcranial electrical stimulation (tES) is a technology that can be made small, lightweight, and non-invasive for deployment in a wide variety of domains. Following hundreds of studies, tES has been shown to improve learning, memory, attention and other cognitive capabilities in healthy subjects, as well as providing benefits in psychiatric and neurological patient populations. However, despite these findings, there remain a large number of unknowns about tES. A better understanding of the effects of tES has the potential for wide-ranging benefits in performance maintenance/enhancement and potentially even therapeutic treatments.

More specifically, the studies conducted over the past decade suggest that low-intensity (e.g., <2mA) transcranial electrical stimulation (tES) can influence behavioral performance on a wide range of tasks. However, there remains uncertainty regarding (1) the significant inter-individual variability in response to brain stimulation, (2) variability in neurophysiological effects regarding brain activity and inter-regional connectivity, (3) the magnitude, nature and duration of immediate- vs. after-effects of stimulation, (4) the role of task-type in response to stimulation, and even (5) the underlying mechanism(s) of the tES effects [1]. Regarding tasks, one domain that has seen particularly limited investigation is the performance of complex tasks that require multiple cognitive capabilities to be used simultaneously. There are numerous examples, but tasks like robotic/teleoperation, navigation, etc. are all relevant. It is unknown what effect tES may have on such tasks, which can be highly relevant for operational settings. **This IRB protocol is designed to support multiple substudies to address the above research questions**.

II. SPECIFIC AIMS

1) Characterize the relationship between the type, location and intensity of stimulation on *behavioral responses*.

2) Characterize the relationship between the type, location and intensity of stimulation on regional *neurophysiological responses*.

3) Characterize the relationship between the type, location and intensity of stimulation on the *after-effects on performance*.

III. SUBJECT SELECTION

Initial substudies will be conducted on healthy volunteers. Later substudies will be conducted on select patient populations (added via protocol amendment).

Healthy volunteers

We will recruit healthy individuals, age 18-64. In some substudies, we will restrict this further to the age range of 25-55 as representative of the astronaut population, given our group's focus on spaceflight-relevant research.

Inclusion criteria:

- Aged 18-64 years.
- No history of head injury or other neurological or psychiatric disorders, particularly bipolar disorder [2].
- No history of cardiac disease, including ischemic heart disease, arrhythmia, hypertension, or syncope.
- No metal implants in the head
- No implanted electronic devices.
- Not taking any drugs known to effect neural or cardiovascular function.
- Ability to give a written and dated informed consent.

Exclusion criteria:

- Smoking within the last year
- Current illegal drug use
- Alcohol abuse
- Pregnancy, as determined by urine pregnancy screening test
- Participation in another brain stimulation protocol within the past month.

IV. SUBJECT ENROLLMENT

The series of studies is projected to start in October 2020 and to end in December, 2025. During this period, we plan to enroll a total of 120 volunteers. This will allow us to conduct a series of preliminary investigations (typically n=20-30) to address the protocol's specific aims as well as to help develop hypotheses for future research.

a. Methods of enrollment, including procedures for patient registration and/or randomization:

Healthy control volunteers will be recruited through postings within the hospital environment, via email bulletin boards, and through engagement with the Rally with Partners program. Additionally, recruitment will extend to individuals who have previously expressed interest in participating in research studies led by the Principal Investigator (PI).

The recruitment procedure will include the integration of a REDCap survey as a preliminary screening tool to assess potential participants' eligibility for study inclusion. Prospective participants will have access to the REDCap survey through various channels, including direct QR code links provided on advertisements and survey links on the Rally page.

Upon accessing the REDCap survey, individuals will be presented with a study description and a link to the Rally webpage for detailed information and direct contact with study staff. Completion of the REDCap survey will serve as an initial step in the recruitment process. However, individuals expressing interest via the Rally page can opt for phone calls for initial screening. If this is preferred, a direct phone call will be made to the subject. Contact information for direct communication with study staff will be provided to individuals expressing interest in participating, regardless of completing the REDCap survey, to accommodate a preference for direct contact. Following completion of the initial screening, participants who meet the initial eligibility criteria will be contacted via telephone.

b. Procedures for obtaining informed consent (including timing of consent process):
This follow-up will involve more detailed questions to determine suitability for study enrollment, clarifying responses provided during initial screening, and answering any remaining questions they may have about the study. If the individual passes all eligibility criteria and is interested in participating, they will be provided with a copy of the consent form in advance and scheduled for study participation. Upon arrival, volunteers will be brought to the research exam room, where one of the investigators will explain the study in detail. In addition, the volunteer will be introduced to the behavioral tasks, the brain stimulation equipment, and the monitoring equipment to be used. Volunteers will be asked if they have questions about the study and express any concerns. They will also be informed of their right to withdraw from the study at any time. If they choose to participate, we will obtain their written informed consent, which will be countersigned by one of the study investigators.

c. Treatment assignment, and randomization (if applicable):

The study does not involve treatment assignment and/or medications, and each subject undergoing tES will have both active and sham conditions (i.e., they will serve as their own control). Therefore, treatment assignment and randomization is not applicable.

V. STUDY PROCEDURES

All investigations will involve computerized versions of standardized cognitive tests (e.g., N-back, continuous performance task, reaction time tasks, decision making tasks, spatial cognition, etc.) and/or more complex/operational performance tasks (e.g., robotic teleoperation, driving/navigation, or other computerized task).

Every study will involve two phases: (1) familiarization/training, (2) testing with/without brain stimulation. To address our aims regarding after-effects, some substudies will involve a third phase (3) post-testing without any additional brain stimulation. These phases will be described separately.

Phase 1 – Familiarization/Training: Tasks will be computerized tests that range from approximately 2-60 min in length. These will assess memory, attention, risk tolerance, executive function, and various other cognitive processes, sometimes in combination. For familiarization, subjects will have the computerized tasks explained to them, and then they will practice the tasks. Such familiarization/training sessions will take roughly 5-120 minutes, depending on the

duration and complexity of the task. This phase may be split across separate visits based on scheduling constraints or extent of task training required. Physiological monitoring (see Phase 2) will be conducted during familiarization task performance as well, to help adapt subject to the related sensors. Finally, subjects will be familiarized with the tES device, setup, and "feel". This will involve full rigging and then experiencing a "sham" stimulation condition which includes the ramp-up, less than 30 sec of stimulation, and ramp-down—a condition which generally feels identical to an active stimulation condition.

Phase 2 – Testing: Once familiarization and training is complete, the second phase will involve up to 5 sessions of tES brain stimulation, conducted on 1-5 separate visits (also dependent on the duration of the behavioral tasks and scheduling constraints). Each Testing session will proceed as follows:

Physiological Monitoring Setup: If applicable, subjects will first be rigged for physiological recording, including one or more of the following: near-infrared spectroscopy for brain function monitoring, EEG for cerebral electrophysiological monitoring, EMG for muscle monitoring (thumb, arm, and/or cheek), EOG for eye movement monitoring (to detect artifacts in EEG), ECG for heart rate and variability monitoring, respiration, skin temperature, accelerometry and blood pressure. Our group's NINscan-SE device can record all of these simultaneously, using superficial skin sensors which will be coupled to the skin via standard stick-on gel electrodes, or comfortable fabric straps. These will be secured so as not to contact or interfere with the placement of any of the tES electrodes.

tES setup: We will use a Soterix Medical HD-MxN-33 fully programmable system for double-blind stimulation protocols (Soterix Medical, New York, NY) with electrodes attached to custom high-definition plastic holders, filled with saline-soaked sponges or conductive electrolyte gel designed for tES, all embedded in the head cap. Electrode placement will be guided by current-flow modeling using HD-Explore and HD-Targets (Soterix Medical, New York, NY), with sites selected based on prior tES research for that particular type of task (when possible), or other neuroimaging study (e.g., fMRI, fNIRS) that indicates the approximate location of networks involved in the behavioral tasks to be tested. Stimulation intensity (peak to peak) will be set below 2.0 mA (and below 1.0 mA for montages near the temporal bone window). Stimulation will be conducted during the task(s), for no more than 45 min continuously, and for a maximum of 60 min total per day. For tACS at two locations, we will use either in-phase or anti-phase stimulation to enhance or suppress (respectively) brain synchronization and/or connectivity between the two regions [3-6].

tES protocol: Our studies will all be double-blind sham controlled. The exact stimulation protocol will depend slightly on the specific aim we are addressing. However, the stimulation parameters will be restricted to the following:

- *Stimulation type*: direct current (tDCS), alternating current (tACS), or random noise stimulation (tRNS)
- *Stimulation intensity*: range=0.4-2.0 mA; this will generally be ~1.5 mA based on current modeling, but with a maximum of 2.0mA peak current (and a maximum of 1.0 mA for electrodes in the vicinity of the temporal bone window). All stimulations will begin with a 20-sec ramp-up and end with a 20-sec ramp-down period to minimize tingling and itching.

- *Stimulation frequency*: range=1-200Hz for tACS and tRNS only; based on prior findings of tACS enhancement of endogenous oscillations we will use tACS in the 1-40Hz range, and based on prior tRNS findings of performance enhancement on sensory and motor tasks with 100-200Hz oscillations of random amplitudes, tRNS will focus on the 100-200Hz range.
- *Stimulation duration*: range=5-45 min for a single continuous stimulation, with a maximum per day limit of 60 min (i.e., remaining within the low-intensity tES regime [2])
- *Stimulation session repetitions*: range=1-5 (again, remaining within the 60 min/day total stimulation limit); hence a maximum of 5 days of stimulation
- *Stimulation locations*: range=1-3; each subject will undergo tES over 1-3 different brain regions, but no more than 2 brain regions will be stimulated at the same time, always limited as described above.

Each subject will perform the task(s) from their familiarization/training session with stimulation, as well as without stimulation (sham) as part of Phase 2. We will counterbalance orders within/between subjects. A second stimulation period may be repeated on a given stimulation day, within the limits described above. The sham stimulation condition will follow the same procedure as the active condition, but stimulation will last only 30 seconds, ramping up and down at the beginning and end of the period to simulate the tingling sensation that subjects typically experience and then quickly habituate to during active stimulation [7].

Following each session, a safety questionnaire [8] will be administered, including questions regarding attention, concentration, mood, vision, headache, fatigue, and skin sensations under the stimulating electrodes.

Phase 3 - Post-testing: For studies investigating after-effects of stimulation, participants will perform the task(s) with physiological monitoring again without stimulation at up to 6 time points during the following week. Any interval >10 hours will be conducted during a separate visit the following day.

Overall Limits: Again, regardless of stimulation condition (stimulation or task duration, repetitions, or number of brain locations stimulated), no subject will exceed 2.0 mA peak-to-peak, 45 min in a single stimulation session or 60 min/day.

Substudy 1: For this study, our primary outcome will be a 30 min computerized track-and-capture task battery involving dual-hand controllers. Phase 1 will last ~3 hours for consent, familiarization and task training. In Phase 2, subjects will undergo 45 min stimulation (or sham), perform the task battery, another 45 min of sham (or stim) one week later, and again perform the task battery. Stimulation will involve tDCS over the target location with a net intensity of 1.5-1.9mA depending on target and electrode configuration. Sham will involve the same electrode placements and the same 20-sec current ramp-up followed immediately by the 20-sec ramp-down. This generates sensory experiences similar to actual stimulation but without brain stimulation effects. Throughout Phase 2 we will record near-infrared spectroscopy (NIRS) over the prefrontal cortex, as well as 2-channel EEG (F3/F4), 1-channel ECG, 1-channel EMG, respiration, blood pressure, accelerometry and skin temperature. For Phase 3, subjects will be asked to return on two consecutive days after each stimulation to repeat the task battery and physiological monitoring (no brain stimulation on follow up days). This will result in a total of 7 visits over 11 days (Phase 1=~3 hours on day 1, Phase 2=~3 hours on day 2 and day 9, Phase

3=~1 hour on each of days 3, 4, 10 and 11). For this substudy, N=20 subjects will be stimulated over the left dorsolateral prefrontal cortex (DLPFC), and a separate N=20 subjects will undergo stimulation over the left insular cortex. Electrode configurations for each location will be based on current source modeling with Soterix Medical's HD-Targets modeling software.

VI. BIOSTATISTICAL ANALYSIS

The specific metrics and our methods to calculate them appear below. All metrics will be cross-checked and verified prior to analysis. NINscan-derived measures will be processed programmatically to identify signal quality or dropout issues, any of which will be manually cross-checked, all per our prior work.

Preprocessing:

Performance Data: Behavioral task data will be evaluated per standard methods, typically summarizing accuracy and response time (e.g., [10]) or summarizing various other continuous performance metrics such as smoothness of performance (e.g. [11]). This will provide a range of measures of individual cognitive capacities as well as operationally relevant performance metrics for both sham and stimulation conditions.

NIRS: We will use the modified Beer-Lambert law to compute concentrations of oxy-, deoxy- and total-hemoglobin ([O_2Hb], [HHb], and [HbT] respectively). Close-detectors measuring scalp-only signals will be used as regressors to filter out systemic effects in most cases. The resulting data will be used to compute task-related functional activation, resting cardiac and vasomotor pulsatility, and inter-hemispheric functional connectivity at resting baseline, all per prior work [12-15].

Systemic Physiology: For ECG, we will compute average heart rate and heart rate variability via peak-detection algorithms. Respiratory rate and volume can be computed from the respiratory sensor. The accelerometer will be fed through a standard actigraphy algorithm [16]. EEG will be examined through power spectral analysis after band-filtering to the frequencies of interest (e.g., 0.1-40 Hz).

Analysis:

We will first use descriptive statistics (means, standard deviations, skew, kurtosis) to characterize each metric within each subject and condition. Given the known speed-accuracy trade-off, we will make response time and accuracy the primary measures for each task (other metrics being secondary). We will then quantify the relationships between behavioral responses (Aim 1), neurophysiological responses (Aim 2) and after-effects on behavioral performance (Aim 3) as a function of type, location, intensity, and duration of brain stimulation. This will be conducted via mixed effects linear modelling approaches, with appropriate follow-up testing, including linearity, calibration, additivity, outliers, and post-hoc analyses to help identify nonlinearities such as onset of effects as a function of stimulation duration or intensity, and so forth.

We will report all p-values as uncorrected but include the number of statistical tests performed.

VII. RISKS AND DISCOMFORTS

Near Infrared Spectroscopy: NIRS monitoring requires coupling optodes to the skin on the scalp. This is achieved by fastening the optodes to a stretchy cap or strap, and positioning that over the target portion of the head. The subject's hair may need to be parted in the location of the optodes to provide better coupling to the skin. The procedure does not cause pain or distress, although extended wearing of the device may lead to discomfort due to the mild pressure. The instrument will be made as insensitive as possible to head motion, and hence there are essentially no restrictions on head motion. Near Infrared Spectroscopy (NIRS) is an investigational tool and although no adverse effects have been reported, it is possible that effects not yet reported may occur. The NIRS devices use low power laser diodes emitting light at 780 and 830 nm. As such, there are general risks associated with laser use including over-exposure of the skin or eyes. The optical power delivered to the skin of the subject is P ~ 12mW. Since this power is distributed over an area of 3 mm or more, $A=\pi(0.3/2)^2$ cm^2, the optical fluence at the skin is $P/A \sim 0.17 W/cm^2$. This value is smaller than the maximum permissible exposure (MPE) for skin exposure to a laser beam, as indicated by the American National Standards Institute (see the ANSI Standard Z136.1, Table I). The MPE indicated by the American National Standards Institute (ANSI) standards for skin exposure ranges from $0.2 W/cm^2$ at 690 nm to $0.4 W/cm^2$ at 850nm. Moreover, the CW-NIRS laser light is not collimated and diverges in a wide angle (>50 deg) at the probe end because of an optical diffuser attached to the laser output window. This would result in a Nominal Ocular Hazard Distance (NOHD) of less than 5 cm, which is lower than the 10 cm focusing distance of the retina. Hence, the NIRS devices connected to the probes do not necessitate eye protection.

Transcranial electrical stimulation: It is expected that a minority of subjects will experience tingling and/or itching beneath the electrodes during stimulation, or potentially post-stimulation fatigue, mild headache, or local discomfort. Less commonly, subjects may experience nausea and in rare cases subjects have been reported to experience insomnia. In very rare cases, skin burns could be experienced due to inappropriate direct contact of electrodes with the skin.

EEG/EMG/ECG/EOG/respiration monitoring requires coupling a sensor to the skin via electrodes. This can cause skin irritation.

Behavioral testing: There are no risks associated with the behavioral testing aside from the possibility of fatigue or boredom. Time periods between data collection will be subject-controlled in an attempt to reduce both.

VIII. POTENTIAL BENEFITS

There are no direct benefits to the participants in this study. The investigators hope that successful completion of this series of substudies will provide a significantly improved, systematic understanding of the relationship between tES parameters (location, intensity, and type of stimulation) and (i) neurophysiological brain responses, and (ii) behavioral effects, both immediate and over time.

IX. MONITORING AND QUALITY ASSURANCE

The integrity of tES electrodes must be checked every session and the electrode impedance needs to be continuously monitored to ensure adequate electrical coupling with the skin. All tES stimulation protocols will be double-checked by a second experimenter prior to implementation to ensure they comply with protocol limits described above. Given the low light powers involved in near-infrared spectroscopy, the NIRS system is considered a non-significant risk device.

X. REFERENCES

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