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Tolerability of Repeated Application of Transcranial Electrical Stimulation with Limited Outputs to Healthy Subjects

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ABSTRACT

Background: The safety and tolerability of limited output transcranial electrical stimulation (tES) in clinical populations support a non-significant risk designation. The tolerability of long-term use in a healthy population had remained untested.
Objective: We tested the tolerability and compliance of two tES waveforms, transcranial direct current stimulation (tDCS) and modulated high frequency transcranial pulsed current stimulation (MHF-tPCS) compared to sham-tDCS, applied to healthy subjects for three to five days (17–20 minutes per day) per week for up to six weeks in a communal setting. MHF-tPCS consisted of asymmetric high-frequency pulses (7–11 kHz) having a peak amplitude of 10–20 mA peak, adjusted by subject, resulting in an average current of 5–7 mA.
Method: A total of 100 treatment blind healthy subjects were randomly assigned to one of three treatment groups: tDCS (n = 33), MHF-tPCS (n = 30), or sham-tDCS (n = 37). In order to test the role of waveform, electrode type and montage were fixed across tES and sham-tDCS arms: high-capacity self-adhering electrodes on the right lateral forehead and back of the neck. We conducted 1905 sessions (636 sham-tDCS, 623 tDCS, and 646 MHF-tPCS sessions) on study volunteers over a period of six weeks.
Results: Common adverse events were primarily restricted to influences upon the skin and included skin tingling, itching, and mild burning sensations. The incidence of these events in the active tES treatment arms (MHF-tPCS, tDCS) was equivalent or significantly lower than their incidence in the sham-tDCS treatment arm. Other adverse events had a rarity (<5% incidence) that could not be significantly distinguished across the treatment groups. Some subjects were withdrawn from the study due to atypical headache (sham-tDCS n = 2, tDCS n = 2, and MHF-tPCS n = 3), atypical discomfort (sham-tDCS n = 0, tDCS n = 1, and MHF-tPCS n = 1), or atypical skin irritation (sham-tDCS n = 2, tDCS n = 8, and MHF-tPCS n = 1). The rate of compliance, elected sessions completed, for the MHF-tPCS group was significantly greater than the sham-tDCS group's compliance (p = 0.007). There were no serious adverse events in any treatment condition.
Conclusion: We conclude that repeated application of limited output tES across extended periods, limited to the hardware, electrodes, and protocols tested here, is well tolerated in healthy subjects, as previously observed in clinical populations.

Introduction

Transcranial electrical stimulation (tES) using limited-output current intensities has been explored in healthy individuals as a tool to modulate cognitive performance [1–11]. Based on a wealth of prior evidence, limited-output tES is typically well tolerated and poses no significant risk to healthy populations [11–13]. However, the preponderance of evidence from healthy volunteers stems from studies testing ten or less tES treatment sessions [7]. The safety and tolerability of repeated use of tES for extended times (e.g. several sessions per week over several weeks) has been limited to studies in clinical populations.

In both normal and clinical populations, repeated use of tES has been proposed to increase efficacy through cumulative effects [14–16]. For example, repeated tES sessions have been demonstrated to increase clinical outcome in therapeutic studies [17,18]. With increasing research on tES to modulate cognition, as well as commercialization efforts, there have been concerns that the rate of testing has outpaced the data on tolerability [19–24].

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In the context of reviewing tolerability, we include prior limited-output "tES" studies regardless of intent to directly modulate the cortex (e.g. transcranial random noise stimulation [25–28]) or cranial nerves (e.g. cranial TENS). Based on this historical data, repeated use of tES on healthy individuals is not expected to pose any significant risks as evidenced by: 1) repeated treatment sessions in clinical populations [29]; 2) acute studies applying a single or few treatment sessions in healthy subjects [1,30–37]; and 3) absence of any evidence for brain injury risk [38,39] though concerns about tradeoff in acute cognitive performance have been raised [40–42]. However, the dearth of data on the tolerability of repeated tES in healthy subject over an extended period of time has been cited as a limitation in informing human trials, as well as the use of tES for lifestyle and wellness applications [19–24]. Therefore, we monitored the tolerability of tES used repeatedly, three to five days per week, in a communal setting for up to six weeks by healthy volunteer subjects.

The tolerability of any tES technique is specific to: 1) session dose (electrical waveform properties and electrode montage) [43], and session repetition number/frequency; 2) electrode design [35,44]; and 3) subject exclusion and treatment protocols. We tested two limited output tES waveforms in addition to an active sham-tDCS waveform: transcranial direct current stimulation (tDCS) and modulated high-frequency transcranial pulsed current stimulation (MHF-tPCS). tDCS was applied at 2 mA, the highest dose commonly used. MHF-tPCS employs modulation designed for painless stimulation with peak intensity at 10–20 mA, adjusted by the subject. As our study was designed to evaluate the influence of different waveforms on tolerability and compliance, all other factors were fixed across study arms including electrode type and montage. Therefore, supporting both tPCS and tDCS, high-performance self-adhesive electrodes were positioned on the right temple and paraspinal area of the neck, allowing high-throughput and reliable electrode preparation, using simple landmarks (none neuro-navigated).

All tES and sham-tDCS sessions were conducted in a communal environment ("coffee shop" lounge setting). Adverse events, adverse reactions and subject-elected compliance were assessed for up to six weeks of repeated tES involving three to five sessions per week. The study included assessments on the effect of tES on State–Trait Anxiety Inventory which will be analyzed elsewhere.

Methods

Participants

The study was conducted in accordance to protocols and procedures approved by the Institutional Review Board of the City College of New York. All volunteer participants provided written informed consent to participate in the study. All subjects were between the ages of 18 and 40 (M = 23, SD = ±5). Transcranial electrical stimulation has been applied to both male and female participants in numerous published studies and no significant gender differences have been reported so both males and females were recruited for this study. The study included 100 healthy individuals (male = 63, female = 37) with no recent history of neurological or psychiatric conditions (past 36 months, see below). All subjects were recruited through local advertisement and financially compensated for their participation.

Screening and exclusion criteria

Participants were excluded if they presented with any skin disorder at or near stimulation locations that compromised skin integrity, such as eczema, rashes, blisters, open wounds, burns including sunburns, cuts (e.g. due to shaving), or other skin defects, as the goal of this study was not to determine if skin impairments influence the tolerability of tES [45]. Mild acne, even if treated by medication, that does not compromise the integrity of the skin and non-irritating skin disorders (for example, vitiligo) were not used as exclusion criteria if there were otherwise no skin lesions in or around the areas where electrodes are positioned. Subjects were excluded if they reported any communicable skin disorder, even if outside the stimulation area.

Participants were excluded if they were currently under treatment for neuropsychiatric disorders as the study aimed to: 1) not evaluate clinical treatment outcomes; 2) avoid unrelated adverse events during the six-week intervention; 3) avoid variations in adverse event reporting across patient populations [37,46]; 4) avoid any theoretical interactions with medical treatments. Participants with a history of neurological or psychiatric disorders must have been off any treatment medications for minimum of 3 years (36 months) to be considered for the study. Participants were excluded from consideration if they had suffered from any form of severe head trauma (for example, head injury or brain surgery) or had any medical devices implanted in the head (such as, a deep brain stimulator) or in the neck (such as, a vagal nerve stimulator).

Subjects were excluded if they suffered from chronic headaches or migraines (headaches or migraines that occurred for consecutive days and are longer than an hour) or had any change in the rate or severity of head pressure, headache, or migraine in the past two weeks. Specifically, two headaches above the subject's typical rate for a two-week period, or two headaches in the past two weeks above the typical severity, or a single headache in the past two weeks with unusually high severity was considered for the exclusion criteria. Such subjects were excluded to minimize possible confounding of naturally occurring headaches with adverse events.

The exclusion criteria were evaluated by self-reported survey for each subject before enrollment in the study and periodically during the study. Before the beginning of the study, the subjects underwent a brief 2 min tES test session corresponding to the experimental arm they were assigned to. If subjects reported a high pain score or a desire not to proceed they were excluded. Based on the screening criteria, 8 subjects were excluded from the study from a total of 108 participants.

Experimental design and tES treatment conditions

The study consisted of a randomized single-blind between-subject design with two experimental conditions and one control condition. The three conditions (for tES waveforms see below) were sham-tDCS-tDCS (n = 37), tDCS (n = 33), and tPCS (n = 30). Electrodes were applied and stimulation was activated by trained research assistants. During recruitment, the subjects were informed that the study would test the tolerability and efficacy ("mental energy and mind states") of different types of neuromodulation stimulation.

Over a six week period, subjects participated in three to five sessions per week (weekdays only) with a minimum of 16 hours between sessions. Subjects were required to complete a minimum of eight sessions in each two-week period throughout the study to continue participation. Except for screening and verbal questionnaires (which were conducted in private), all treatment sessions were conducted in a communal environment designed to provide a lounge or "coffee shop" feel. The experimental space for this study consisted of an open floor plan with both tables and lounge seating. Subjects were allowed to do work on their laptops, had access to magazines, or could engage in quiet discussions with one another.