

The tolerability of transcranial electrical stimulation used across extended periods in a naturalistic context by healthy individuals.

Bhaskar Paneri^{1*}, Peter Toshev^{1*}, Niranjana Khadka¹, Vaishali Patel¹, Chris Thomas¹, William J. Tyler², Lucas Parra¹, and Marom Bikson^{1#}

¹Department of Biomedical Engineering, The City College of New York, CUNY, 160 Convent Ave., New York 10031, USA

²School of Biological and Health Systems Engineering, Arizona State University, Tempe, Arizona 85287 USA

Transcranial electrical stimulation (tES) is one of the most widely implemented forms of non-invasive neuromodulation in basic and clinical neuroscience. Further, the use of tES by healthy populations for various purposes is growing widespread daily. The effects of tES protocols on the skin and other tissues has remained uncharacterized when used across extended periods of time by healthy individuals. Therefore, we examined the basic safety and tolerability profile of two distinct tES protocols used repeatedly across an extended period of time by healthy subjects and report our findings here for the first time. The safety and tolerability profile previously accumulated regarding extended use of tES in clinical populations is compelling and supports a low-risk or non-significant risk designation. In the present study, we tested the tolerability (safety) and compliance, compared to sham, of two common tES approaches having a current density $< 2 \text{ mA/cm}^2$; transcranial Direct Current Stimulation (tDCS) or transcranial Pulsed Current Stimulation (tPCS) used by healthy subjects three to five days (17 - 20 minutes per day) per week for up to six weeks in a naturalistic environment. In this study 100 healthy subjects were randomized to one of three treatment groups: tDCS ($n = 33$), tPCS ($n = 30$), or sham ($n = 37$) and blinded to the treatment condition. The tES and sham waveforms were delivered through self-adhering electrodes on the right lateral forehead and back of the neck. We conducted 1905 treatment sessions (636 sham, 623 tDCS, and 646 tPCS sessions) on study volunteers over a six-week period. There were no serious adverse events in any treatment condition. Common side effects were primarily restricted to influences upon the skin and included skin tingling, itching, and mild burning sensations. The incidence of these events in active tES treatment arms (tPCS, tDCS) was equivalent or significantly lower than their incidence in the sham treatment arm. Other adverse events had a rarity ($< 5\%$ incidence) that could not be statistically distinguished across the treatment groups. Some subjects withdrew early from the study for atypical headache (sham $n = 2$, tDCS $n = 2$, and tPCS $n = 3$), atypical discomfort (sham $n = 0$, tDCS $n = 1$, and tPCS $n = 1$), or atypical skin irritation (sham $n = 2$, tDCS $n = 8$, and tPCS $n = 1$). The compliance (elected sessions completed) for tPCS was significantly greater when compared to sham ($p = 0.007$). The present study represents the most comprehensive analysis of tES tolerability and safety in healthy subjects to date. Limited to the hardware, electrodes, and protocols tested here, we conclude that repeated use of limited output tES across extended periods, is well tolerated and poses no significant risks to healthy subjects, as previously observed in clinical studies.

INTRODUCTION

Transcranial electrical stimulation (tES) using limited-output current intensities [1], has been explored in healthy individuals as a tool in cognitive neuroscience [2–7] and to accelerate learning [8] or enhance cognitive performance [9–14]. We note the term “transcranial” in the context used here does not necessarily imply a direct mechanistic action of electrical current delivered across the cranium, since it also encompasses transdermal modulation of cranial nerves (that pass through foramina of the skull) and spinal nerves. Based on a wealth of prior evidence, low intensity or limited-output tES is typically well tolerated (painless) and poses no significant risk to healthy populations. However, the preponderance of this evidence stems from acute use studies investigating

healthy volunteers, who undergo only a single or at most a few tES treatment sessions. The safety and tolerability of repeated use of tES across extended times (e.g. several sessions per week over several weeks) has been limited to study in clinical populations.

In both normal and clinical populations, repeated use of tES has been proposed to increase efficacy through either cumulative effects of the modulation itself [15,16] or the cumulative effects of any adjunct training [17]. For example, repeated tES sessions have been demonstrated to increase clinical efficacy in therapeutic studies [18,19]. With the escalating research use of tES to modulate cognition in healthy subjects and the commercialization of technologies marketed for consumer use, repeated tES use by healthy populations is becoming widespread. Therefore

*Authors contributed equally

#Correspondence: marom.bikson@gmail.com

it is critical to investigate the safety and tolerability of repeated tES in healthy subjects.

Based on the studies reported thus far, repeated use of tES on normal subjects and by healthy individuals is not expected to pose any significant risks as evidenced by: 1) repeated treatment sessions in clinical populations [19, 20]; 2) acute studies applying a single or few treatment sessions in healthy subjects [9,21–28]; and 3) absence of any established theoretical risk [29,30]. None-the-less, empirical observations on the safety and tolerability of repeated tES across an extended period by healthy volunteers would inform ongoing trials and future studies, as well as individuals interested in the use of tES for lifestyle and wellness applications including for modulation of psychophysiological arousal or cognitive and mood enhancement [31–33]. Therefore we monitored the safety and tolerability of tES used repeatedly (three to five days per week) in a naturalistic setting for up to six weeks by healthy volunteer research subjects.

The tolerability of any tES technique is specific to: 1) dose, namely electrical waveform properties and electrode montage [34]; 2) electrode design [27,35]; and 3) subject exclusion and treatment protocols. We tested two waveforms of limited output tES including tDCS and tPCS, as well as an active sham waveform. All other factors, such as electrode types, electrode montages, and treatment session times were identical across arms to evaluate the influence of different waveforms on tolerability and compliance. 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 nd sham sessions were conducted in a naturalistic communal environment (“coffee shop” or lounge type of setting). Adverse events, adverse reactions and subject-elected compliance was assessed for up to six weeks of repeated tES involving three to five sessions per week. The study included assessments on mood, reported separately except as relevant for tolerability. We found repeated use of tES as applied in this study to pose low risks and be well tolerated by a population of healthy volunteers.

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 (IRB Protocol #592792-10). All volunteer participants provided written informed consent to participate in the study. Inclusion required subjects to be 18 years or older. Transcranial current stimulation has been applied to both male and female participants in numerous published studies and no significant gender differences have been reported. We recruited 100 healthy individuals (63% males and 37% females) with no recent history of neurological or psychiatric conditions.

Screening and Exclusion Criteria

Participants were excluded if they presented with any skin disorder at or near stimulation locations (where

electrodes are placed) that compromised skin integrity, such as eczema, rashes, blisters, open wounds, burn including sun-burns, cuts (e.g. due to shaving), or other skin defects. Our goal was not to determine if skin impairments influence the tolerability of tES [36], and we aimed to avoid ambiguity about the source of any skin irritation by only including subjects with intact skin. Participants on acne medication for mild acne that does not compromise the integrity of the skin and/or have a non-irritating skin disorder (for example, vitiligo) were not be excluded if there are otherwise no skin lesions in or near the areas where electrodes are positioned. Subjects were excluded if they reported or presented any communicable skin disorder even if outside the stimulation area; though there is no evidence tES aggravates such disorders, it was considered a confound and risk for other subjects in the communal stimulation setting.

We included healthy subjects who were not under treatment for neuropsychiatric disorders though there is no evidence this increases risk to tES/tDCS; [30,37] because in our study: 1) did not evaluate clinical treatment outcomes, 2) we aimed to avoid unrelated adverse effects during the six-week intervention, 3) we wanted to avoid variations in adverse event reporting across patient populations [38,39,4] we wanted to avoid any theoretical interactions with medical treatments. Participants with a history of neurological or psychiatric disorder 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 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 suffer from chronic headaches or migraines (headaches or migraines that occur for consecutive days and are longer than an hour). In addition, if a subject has had a change in the rate or severity of head pressure, headache, or migraine in the past two weeks, they are excluded. Specifically we considered either two headaches above the 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 to be exclusion. Such subjects were excluded to minimize possible confusion of naturally occurring headaches with adverse events.

The exclusion criteria were evaluated for each subject before enrollment in the study and throughout the continuation of the study. The initial pre-screening included a questionnaire for inclusion/exclusion criterion and, if all other criterion met, a brief test session where two minutes of treatment was applied with a waveform corresponding the putative arm they would be assigned to. If subjects reported a high pain score or desire not to proceed after the two-minute stimulation screen they were excluded; otherwise, they were enrolled in the study.

Experimental Design and tES Treatment Conditions

The study was conducted using a between-subject design where 100 subjects were assigned to one of three experimental conditions and were always kept blind to their assigned condition. The three treatment conditions (for tES waveforms see below) were placebo or active sham (n = 37), tDCS (n = 33), and tPCS (n = 30). Over six weeks, subjects scheduled to participate in three to five sessions per week (weekdays only) with a minimum of 16 hours between sessions. Subjects were required to complete minimum of eight sessions in each two-week period throughout the study to continue participation. Except for screening and any verbal questionnaires (which were conducted in private), all treatment sessions were conducted in a naturalistic environment designed to provide a lounge or “coffee shop” feel. Figure 1 illustrates the naturalistic space dedicated to this study with an open floor plan with tables and lounge seating. Subjects were allowed to do work on their laptops, had access to magazines, could engage in quiet discussions with one another, and had access to the internet over a provided Wi-Fi network.

The placebo or sham treatment protocol was to deliver a 30 sec linear ramp of current up to 2 mA and immediately back down to 0 mA over 30 sec at the start of the session and again 20 minutes later at the end of the session. We used a Soterix Medical 1x1 tDCS to provide placebo stimulation through electrodes (see below). The tDCS treatment waveform was delivered with battery-driven, medical-grade tDCS devices with Limited Total Energy (1x1 tDCS, Soterix Medical Inc. New York, NY). Current was linearly ramped up across 30 sec to 2 mA, maintained at 2 mA for 20 minutes, and then linearly ramped down to 0 mA across 30 sec. The tPCS waveforms were delivered with battery-powered, medical-grade Transdermal Electrical Neurosignaling (TEN) devices (Thync, Inc., Los Gatos, CA) programmed to produce pulse-modulated (7 – 11 kHz), biphasic electrical currents producing average amplitudes of 5 – 7 mA for 17 minutes. Subjects were instructed to adjust the current output of the wearable TEN devices using an Apple iPod Touch connected to the device over a Bluetooth Low Energy network such that it was comfortable.

Electrodes and Montages

The electrodes used for all treatments were self-adhering hydrogel electrodes (Axelgaard Pals® Platinum Blue Electrodes, Axelgaard Manufacturing Co. Ltd, Fallbrook, CA). A rectangular anode electrode (4 x 9 cm) was placed on the right temple of subjects after asking them to bite down for reference. The third of the electrode (landscape orientation reference) which had the wire attached was positioned over the right temple (Figure 2). The other two thirds of the electrode was positioned towards the forehead above the eyebrow at an angle $\theta = 45$ degree (from a plane parallel to the floor). According to the international 10-20 electrode positioning system, the electrode approximately spans approximately from F₈ to F_{pz} [40]. As deemed useful, on some subjects adhesion was reinforced with a headband (Universal Strap, Caputron Medical Inc.). A square cathode electrode (5 x 5cm) was

positioned on the base of the neck and aligned such that the middle of the electrode was 1 cm to the right of the subject’s middle line. The electrode position was approximately above the cervical spine vertebrae C7. As deemed useful, on some subject adhesion was reinforced with light medical tape. In some cases an elastic head-strap was used to help fix electrodes (Caputron Medical, Universal Strap). The forehead electrode was positive polarity relative to the neck reference electrode. Electrodes were used for a single session and discarded afterwards. Electrode locations on the forehead and the neck are shown in Figure 2. The electrode impedance was checked prior to stimulation and electrodes were adjusted as needed.

Subject Monitoring, Adverse Events, Adverse Reactions, and Withdrawal Criteria

We adopted a conservative approach to adverse event and adverse reaction assessment, as well as study withdrawal. Redundant methods of assessment were used with a bias toward detecting positive responses, either true or false (for example if a subject did not report headache in questionnaires, but did on screening bridge). Subjects were withdrawn for “atypical” adverse events, even if not evidently hazardous and without consideration if the event was related to study participation. Adverse events, adverse reactions, and study withdrawals were sub-classified into within-session or between-session occurrences. Subject status was rigorously monitored including: 1) A ‘screening bridge’ where all inclusion/exclusion criterion were reevaluated every two weeks along with a Short Form 36 Health Survey (SF-36); 2) Detailed adverse event and adverse reaction questionnaires were administered before and after each treatment session; 3) Visual inspection the skin was conducted before and after each treatment session; 4) Encouraging subjects to report adverse events or adverse reactions on an ongoing basis; and 5) Subject re-consent at the start of each session.

The withdrawal criteria are listed below:

- 1) Subjects experiencing any adverse event requiring medical intervention were excluded. Subjects were withdrawn if they experienced a serious adverse event defined based on the Neuromodoc 2014 consensus based on International and US guidelines on serious adverse events from medical devices (including the Office of Human Research and Protection (OHRP) of the U.S. Department of Health And Human Services (HSS); FDA regulations at 21 CFR 312.32[a]; 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice; ISO/DIS 14155-Clinical investigations of medical devices in humans, good clinical practices, 2008). A severe adverse event related to stimulation was a documented event that:
 - a. Based upon scientific judgment determined to be at caused or aggravated by the application of direct current to the head AND
 - b. Results in irreversible damage of brain tissue OR

- c. Results in persistent disability or incapacity that produces an unwanted and substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in an unwanted significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life OR
- d. Results in inpatient hospitalization or prolongation of existing hospitalization, where emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event) OR
- e. Results in death or is life-threatening where the patient was at substantial risk of dying at the time of the adverse event, or use was discontinued based on evidence tDCS might have resulted in death OR
- f. Medical or surgical intervention was necessary to preclude permanent imminent impairment of a body function due to stimulation, or prevent permanent damage to a body structure due to stimulation.

It is important to note that no severe adverse events occurred or were documented in any treatment condition during this study.

- 2) Change of status exclusion: Throughout the study if any subject failed to meet study inclusion/exclusion criteria, including changes in medical diagnosis or treatment they were excluded from the study. The only withdrawals for changes of status occurred for atypical skin condition and atypical headache. We note one subject in Sham arm presented hives on their arms and not on electrode region. The subject was withdrawn by session 13 when the hives were discovered. This was criterion for withdrawal based on 'atypical skin condition' but not a serious adverse event.
- 3) "Atypical skin condition": In addition to exclusion based general skin health (for example, communicable diseases), we adopted a conservative approach for subject withdrawal based on even minor skin irritation under the electrode areas, regardless of presumed associated with stimulation (for example, shaving irritation). Skin was visually inspected prior to and after each session by the investigator [41,42]. Prior to stimulation, moderate to severe erythema (that had persisted since the last session), but not slight erythema, was reviewed for withdrawal. Erythema after stimulation was not, in itself, criterion for withdrawal unless severe. Prior to stimulation, minor edema (for example, defined raising around

electrode area) was reviewed for withdrawal. Moderate edema after stimulation (for example, area swollen/definite raising) was reviewed for withdrawal. Minor spotting (petechial) was not criterion for withdrawal. A blister (> 1 mm) was a criterion for withdrawal. Review for withdrawal was based on skin irritation that appeared cumulative, namely the skin is altered from the prior session in way that will influence skin response to the current session and next. Though not injurious [43], we adopted this conservative criterion as preventative. Within-session or between-session withdrawal depended on if the skin irritation was identified immediately before or after the session.

- 4) "Atypical headache": Headaches are expected in the normal population. Our conservative criterion for exclusion was based on unusual or atypical intensity or frequency of headache (see above), regardless of causal link with stimulation. Within-session or between-session withdrawal depended on the time of the last headache.
- 5) "Atypical Discomfort": If during stimulation, subject expressed a desire to terminate the stimulation session for discomfort, stimulation was aborted and subjects were withdrawn from the study - regardless of their desire to continue with future sessions. If subjects indicated moderate discomfort (for example, based on their prior sessions experience) but desire to continue with the session, stimulation was ramped down, electrode were adjusted, and stimulated re-started. If a subject was reluctant to under stimulation because of discomfort between-session they were withdrawn- there were no such cases in this study.

Adverse events and adverse reactions were also assessed through self-reporting questionnaires completed before each session for "between-sessions" effects (adverse events that persisted after the last treatment or occurred at a time since the last session) and after each session for "within-session" effects. For each evaluation we queried subjects twice with one open-form response and one adverse-event index. For open form, lexical analysis mapped response to any of the indexed adverse-events or classified as "anecdotal". The lexical analysis was conducted using customized PHP software built in house which categorized and tallied all the different adverse events. In addition, the algorithm was designed to take into account positive and negative connotation of the reposted adverse events. In the end, the open ended text was also checked manually by human to find any mistakes in the tallied reports or to find additional adverse events not detected by algorithm. Itemized adverse-events encourage responsiveness in tDCS ([27]) while open form response allow for uncategorized response or individual terminology. We based our indexed events on common reported tDCS adverse events [21,23,38], selecting for items that were specific in etiology (for example, "skin tingling" as opposed to "discomfort") and conducive to self-reporting (for example, skin redness was only

accessed by the investigators). Indexed adverse reactions and adverse events were: 1) skin tingling; 2) skin itching; 3) skin burning sensation; 4) nauseous; 5) diffuse or migraine-like headache; 6) facial muscle twitching; 7) blurred vision; 8) short-lived localized head pain or pressure; 9) forgetfulness; 10) difficulty concentrating; 11) dizziness; 12) difficulty breathing. Incidence of adverse events or reactions were coded in binary system (no = 0, yes = 1). For within-session evaluation participants scored the severity (1 = minimal; 4 = mild; 8 = moderate; 10 = severe) and duration (minutes) of each event.

The subject's state anxiety level was measured using an abbreviated version of the State Trait Anxiety Inventory containing six statements (STAI-6) according to scoring guidelines [44]. The STAI-6 questions were: 1) I feel calm; 2) I am tense; 3) I feel upset; 4) I am relaxed; 5) I feel content; 6) I am worried. The delta STAI-6 score was calculated by subtracting the total post-questionnaire STAI-6 score from the total pre-questionnaire STAI-6 score.

Adverse events were categorized both session-wise, aggregating across subjects (Table 1) and subject-wise with likelihood of adverse event (percent) collapsed across session for each subject (Figure 3) with statistics only possible on the later.

Statistical Tests

Before applying any statistical test, the data sets were tested for a normal distribution. The normality was measured by the analysis of skewness and kurtosis. If the skewness for the data is more than twice the standard error of skewness and the kurtosis for the data is more than twice the standard error of kurtosis then the data set is normally distributed [45]. If the data was found to be normally distributed, then one-way ANOVA and t-test was used for the comparison. If the data was found to be not normally distributed then Kruskal-Wallis test or Mann-Whitney rank-sum test was used for the comparison [46]. In order to correct for multiple comparisons, Benjamini-Hochberg procedure was used to further validate the significance of each p-value. The α -value was set to 0.05 for all the statistical tests and Benjamini-Hochberg procedure. Table 1 shows mean \pm standard deviation and the error bars in Figures 3 and 7 are shown as standard error of the mean.

RESULTS

Compliance and Withdrawal

We conducted and observed a total of 1905 treatment sessions (sham = 636, tDCS = 623, and tPCS = 646) on a total of 100 subjects (sham = 37, tDCS = 33, and tPCS = 30). No severe adverse events were reported. Including all subjects, the average number of sessions completed by subjects in each study arm was 17.2 ± 8.1 (SD) for sham, 18.7 ± 7.8 for tDCS, and 21.5 ± 6.7 for tPCS treatment groups. The total number of sessions completed by subjects in tPCS arm were significantly ($p = 0.007$) greater compared to the sessions completed by participants in the sham group; no other completion comparisons were significant. Excluding subjects that withdrew, the average

number of sessions completed by subjects in each study arm was 18.5 ± 7.5 (SD) for sham, 21.6 ± 7.6 for tDCS, and 23.6 ± 5.3 for tPCS. Excluding withdrawn subjects, the number of sessions completed by subjects in tDCS ($p = 0.03$) and tPCS ($p = 0.0009$) arms were significantly greater than the number of sessions completed by subjects in sham treatment group.

The data shown in Table 2 summarizes treatment session counts and withdrawal rates. For "Atypical Discomfort", there was one incidence of a subject requesting a stimulation session to be stopped once initiated in the tDCS arm (after subject successfully completing 21 prior sessions) and one such incidence in the tPCS arm (after subject successfully completing 20 prior sessions). In both cases, operators indicated that an electrode was not uniformly adhered to the skin. In both cases subjects indicated a desire to remain enrolled in the study.

Subject self-reports of "atypical headache or migraine" (increased frequency or severity, see Methods) resulted in the study withdrawal of two subjects in the sham group, two subjects in the tDCS group, and three subjects in the tPCS group. In all cases these withdrawals reflected adverse events occurring between, not during, sessions. The number of treatment sessions completed prior to withdrawal for the atypical headache or migraine events were: sham = 10 and 3 sessions for the two subjects; tDCS = 19 and 10 sessions for the two subjects; and tPCS = 22, 9, and 8 sessions for the three subjects.

In some cases, inspection of skin resulted in study discontinuation due to "atypical skin condition" (using the conservative thresholds described in Methods). Atypical skin conditions resulted in study discontinuation for two subjects from the sham group, eight subjects from the tDCS group, and one subject from the tPCS group. One subject in the sham arm was excluded after presenting hives on their arms, not near electrodes on their thirteenth treatment session. Of the remaining subjects withdrawn for atypical skin conditions, one subject in tDCS arm reported skin irritation under neck and forehead electrode while all the other subjects (across arms) reported skin irritation under the neck electrode only. For those subjects with skin irritation under the electrodes, the number of sessions completed prior to withdrawal for an atypical skin condition was: sham = one subject was withdrawn after the first session; tDCS = eight subjects were withdrawn after the 13th, 9th, 14th, 13th, 8th, 12th, 8th, and 14th sessions; tPCS = one subject was withdrawn from the study after the 21st session. In all cases, subjects indicated a desire to remain enrolled in the study.

Tolerability Results

Within-session tolerability was accessed by a questionnaire administered after each session. Between-session tolerability was accessed by questionnaire prior to each session – for the period since the end of the last treatment session including the immediate post-stimulation period. Session-wise data is shown in an aggregated form in Table 1 collapsed across subjects (some subjects received more sessions hence no statistics on session-wise data is reported). Incidence of adverse events

for all treatment groups within treatment sessions was < 3.5% with exception of skin tingling, burning and itching sensations. The incidence of adverse events between treatment sessions was typically < 5%.

Within-session subject-wise data (collapsing across sessions) supported a low (< 7%) incidence rate of all adverse events except the adverse reactions skin tingling, skin itching, and mild skin burning sensation (Figure 3). The incidence of skin tingling in the tPCS treatment group was significantly lower than both sham ($p = 9 \times 10^{-5}$) and tDCS ($p = 0.005$). In addition, the incidence of skin burning sensations in the tPCS group were also significantly lower than sham ($p = 0.006$) and tDCS ($p = 0.003$). There were no other statistically significant differences in the incidence of adverse events across all treatment groups.

In exploratory analyses (Figure 4), we considered the relation between skin tingling, itching, or burning sensations (common side effects) to compliance (number of sessions completed) and withdrawal rate. We found no evident correlations, which indicate adverse event severity of common adverse events (skin tingling, itching, and burning sensations) did not affect compliance rates. We further considered the relationship between severity of skin tingling, itching, or burning sensations and self-reported state anxiety levels (STAI-6 delta score) for each subject. We again found no evident correlations, which indicates the severity of common adverse reactions (skin tingling, itching, and burning sensations) did not affect state anxiety or the reporting of side effects (Figure 5) in this subject-based correlation ($n = 100$). We next explored the session-based relationship ($n = 1905$) between state anxiety levels (STAI-6 delta) and adverse event severity (Figure 6). Session based analyses did not show any significant correlation between state anxiety levels and adverse event severity. These findings are consistent with mild side effects that did not significantly affect compliance or side effect reporting.

We administered a quality of life survey (SF-36 Health Survey) bi-weekly and compared scores across all groups (Figure 7). We did not find a significant difference between the three treatment groups for any of the eight health categories assessed: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Given the SF-36 metrics are gross, they are considered valid for severe quality of life changes across a population. Our observations indicate subjects' general emotional and physical health was not negatively affected by sham, tDCS, or tPCS during the length of the study.

In exploratory analysis, we considered the relationship between within-session and between-session reporting (Table 3). Generally, reporting an adverse event within a stimulation session marginally increased the likelihood of reporting the same event in the follow within-session period. Conversely, reporting an adverse event between-sessions increased the likelihood of reporting the same event during the next stimulation session period. These results are not fully controlled (e.g.

account for carry over effects across many sessions) and do not address causality.

DISCUSSION

Our major finding is that tES is well tolerated and presents low-risk for multiple, repeated sessions in healthy volunteers. To our knowledge, this is the longest duration study examining the safety and tolerability of tES in healthy volunteers to date. Any mild side effects occurring during or between active tES (tDCS or tPCS) sessions were comparable or lower to those observed for sham waveforms. As discussed below, our observations substantiate the low-risk and high tolerability of tES even when used daily on healthy intact skin with proper procedures and medical-grade devices having limited outputs.

General Observations and Compliance

In the present report, we describe the safety and tolerability outcomes of from Naturalistic Extended Use transcranial Electrical Stimulation (NEU-tES). All experimental conditions across arms were fixed except waveform (sham, tDCS, tPCS). Based on prior trials [21,28,47], we developed a comprehensive adverse-event monitoring plan, and implemented conservative (preventative) study withdrawal criterion. We typically could not distinguish between adverse effects and adverse event, i.e. whether side effects were either casual or causal – but for common adverse events we assessed dependence on waveform.

The average number of completed sessions in each arm was: sham = 17.2 ± 8.1 (SD); tDCS = 18.7 ± 7.8 ; and tPCS: 21.5 ± 6.7 . The compliance for tPCS was greater compared to Sham, regardless of whether withdrawn subjects were included or excluded in this analysis. The compliance to tDCS was comparable to Sham including all subjects, and higher when excluding withdraw subject from the analysis. The severity of common adverse events was lowest in the tPCS treatment group. However, within each group we found no relationship between compliance and tolerability (severity of common adverse events). Conservatively, this supports the conclusion that active waveforms (tDCS or tPCS) do not reduce compliance.

Withdrawal and Serious Adverse Events

Across 100 subjects in the three arms there were no serious adverse events were reported with no subject requiring medical care as a result of participating in the study.

With almost 2000 sessions, we report only two cases of discontinuation due to during-stimulation adverse events (one tDCS subject after 21 completed sessions and one tPCS subject after 20 completed sessions). In both cases withdrawal was for “atypical discomfort”. In both cases non-ideal electrode positions was subsequently identified; reduced electrode contact area will increase current density leading to increased sensation. In both cases subjects later indicated desire to resume study participation and presented no other problems. Our observations here are similar to previous findings. There

have been rare reports of mild electrical “shock” occurring with no injury during tES which is associated with abrupt making or breaking of the stimulating circuit [21,28,47].

The remaining withdrawals occurred for events between treatment sessions. The number of subjects withdrawn for between-session headaches was: sham = 2; tDCS = 2; and tPCS = 3. These low withdrawal numbers did not allow for assessment of causality due to treatment especially since headaches occurring following tES occurred at rates similar to sham. Notably, both tDCS and tPCS are investigated for the treatment of headache and migraine [20].

For withdrawals due to atypical skin irritation events, a causal link to study participation was evidenced by the location of irritation under the electrodes. Atypical skin irritation attributed to the electrodes or stimulation occurred in one subject from the sham group, eight subjects in the tDCS group, and one subject in the tPCS group. Irritation from daily application of adhesive electrodes may have irritated the skin in a couple cases, but risk of atypical skin irritation appeared to be increased due to the tDCS waveform being transmitted by the specific electrodes used. The prevalence of irritation under the neck electrode (all cases) suggests increased sensitivity of the skin on the neck region compared to forehead; the neck electrode was marginally smaller and differences in hair follicle density may have contributed to these outcomes. While common in tPCS, the use of adhesive electrodes for tDCS is unusual; sponge electrodes are used in extended tDCS clinical trials with extremely rare occurrence of burns when proper equipment and protocols are employed [38]. We observed no within-session skin injuries. Withdrawal was before stimulation (between-session) reflecting our conservative criterion [35], preventing theoretical injury that might result from cumulative skin irritation. We emphasize that we made no observations of significant skin injury in this study. However, these findings reflect specific equipment and protocols including stimulation across only healthy and intact skin.

Tolerability: skin tingling, itching, and burning sensations

Our dual on-off ramp sham protocol was designed to mimic the sensation of tDCS [38]. During stimulation, mild tingling was the most common adverse event (sham = 70.2 ± 1.8%, tDCS = 55.7 ± 2.0%, and tPCS = 25.8 ± 1.7%). The next most frequent adverse events during stimulation were mild burning or stinging sensations and itching. Mild burning sensations occurred for sham 27.7 ± 1.8%, tDCS 23.3 ± 1.7%, and tPCS 3.4 ± 0.7% of the time while and itching occurred in sham 29.5 ± 1.8%, tDCS 30.9 ± 1.9%, and tPCS 13.5 ± 1.3% of the time. During stimulation, no other adverse events occurred at rates greater than 3.5%. Skin tingling, itching, and burning sensations are all cutaneous nociceptive signals due to stimulation of cranial and cervical spinal nerve afferents that is related to electrode electrochemical performance and skin current flow. In the present trial, we found these sensations occurred during tPCS at significantly lower

rates, which reflects the tolerability and comfort of the waveform/electrode combination used.

Although sensation is waveform and electrode shape/design specific [35], the incidence rates we report for tDCS and sham using adhesive-electrodes are generally comparable to studies of single session tDCS in healthy subjects using sponge-electrodes. Poreisz et al. 2007 reported tDCS to elicit skin tingling, burning and itching sensations in 72.7%, 22.7%, and 36.4% of the cases respectively [23]. Kessler et al. 2012 reported skin tingling, burning and itching sensations due to tDCS occurred at rates of 76.9%, 54.2%, and 68.2% of the time respectively [21].

We observed a trend toward decreasing tingling over the first 2-3 sessions, possibly reflecting accommodation or decreased psychovigilance/stress related to the trial. We found there was no trend toward developed increased sensitivity to sensations across the duration of the trial (Figure 8). The mild skin sensations reported were not associated with withdrawal, which is consistent with prior studies where sensation was not a reliable indicator of other theoretical risks [23].

Headache

The incidence of headache during stimulation (sham = 3.9 ± 0.8%, tDCS 4.4 ± 0.8%, and tPCS 2.6 ± 0.6%) are comparable or moderately lower than reported by prior tES studies [23,38], which could be attributed to range of influences including the naturalistic (relaxed) environment and/or minimal headgear required (due to self-adhesive electrodes) to keep electrodes in place. The incidence of headache between-sessions was 2.4 ± 0.6% for sham, 1.3 ± 0.5% for tDCS, and 1.2 ± 0.4% for tPCS treatment groups. These data illustrate that the theoretical risk of headache due to tES including tDCS and tPCS is low especially considering the incidence rates of headache occurrence was equivalent between active tES treatment and sham.

Other adverse events

Other adverse events occurred at a low incidence rate of < 5%. Especially when one considers that individual subjects underwent a range of number of treatment sessions, these low incidence rates are understood to be imprecise. We can say with confidence these rates are low, and any theoretical difference between arms is still lower. These data further suggest multiple tES sessions across several weeks do not present significant risks to healthy individuals when using medical-grade devices and proper protocols implementing limited outputs at current densities < 2 mA/cm².

Tolerability of daily extended-use tDCS and tPCS by healthy individuals

The outcomes of this study support the safety and tolerability of tDCS and tPCS over repeated sessions in healthy volunteers as compared to sham procedures. Because our goal was to test the role of waveform, all other experimental conditions including electrode design were identical across treatment arms. This compromise represents a limitation of the study because we only

evaluated one type of electrode, which is not commonly used for tDCS procedures. Thus, we speculate the tolerability of tDCS we observed could have been affected by the use of these electrodes although they presented high tolerability rates for tPCS. Based on these observations, it is recommended that investigators choose electrodes that are optimal for the tES waveform being administered. Another limitation is that the sham protocol was designed to produce skin sensation comparable to tDCS, and we discovered tPCS produced less skin sensations. Since differences were small and variable, this would not be expected break naïve subject blinding as to the type stimulation (correct guess of sham, tDCS, or tPCS), but none-the-less [48] warrants consideration in design of future studies.

The occurrence of common adverse reactions (itching, tingling, burning sensation) either decreased or remained stable over weeks. The use of adhesive electrodes produced cumulative skin irritation over the first two weeks in a minority of subjects. These results are broadly consistent with evidence of tolerability from single/limited sessions in healthy individuals [21,23,38] and extended-use in clinical populations [20]. Indeed, transcutaneous electrical stimulators (including transcutaneous electrical nerve stimulators or TENS, powered muscle stimulators, and electrical muscle stimulators) are indicated for a range of clinical/medical purposes (for example, to relieve or treat pain or to improve range of motion) and for cosmetic/aesthetic purposes (for example, to promote muscle toning or skin rejuvenation). These FDA-cleared devices often have current outputs as high as 120 mA and in the case of cosmetic/aesthetic TENS devices can deliver current densities up to 46 mA/cm² while having electrodes placed on the head or face. In contrast, tES current densities are typically < 2 mA/cm² as was the case in the present study. Over the past 40 years, many studies have previously demonstrated the safety and tolerability of electrical stimulation devices used daily for chronic time periods even at those higher current intensities and densities mentioned.

The present study is the most comprehensive study to date evaluating the safety and tolerability of daily use tES in a healthy population. The safety and tolerability of any non-invasive electrical neuromodulation technique is specific to the dose, electrode preparation, and other protocol details. We used medical-grade stimulators with continuous impedance monitoring and waveform controls including limited outputs or limited-total-energy (LTE), adhesive electrodes applied by trained operators, with rigorous monitoring and conservative withdrawal criterion. We emphasize the tolerability of any tES method is dependent on many factors including the protocols used, subject screening and monitoring, tES dose [49], and electrode design/montage [50,51]. Using the protocols and methods described in this report, we found extended use of tES in healthy to pose low-risks and be tolerable across multiple daily sessions.

REFERENCES

- [1] Paneri B, Toshev P, Khadka N, Patel V, Thomas C, Tyler, W.J. et al. The tolerability of transcranial electrical stimulation used across extended periods in a naturalistic context by healthy individuals. n.d.
- [2] Mauri P, Miniussi C, Balconi M, Brignani D. Bursts of transcranial electrical stimulation increase arousal in a continuous performance test. *Neuropsychologia* 2015.
- [3] Nasserri P, Nitsche MA, Ekhtiari H. A framework for categorizing electrode montages in transcranial direct current stimulation. *Front Hum Neurosci* 2015;9:54.
- [4] Elmasry J, Loo C, Martin D. A systematic review of transcranial electrical stimulation combined with cognitive training. *Restor Neurol Neurosci* 2015. doi:10.3233/RNN-140473.
- [5] Miniussi C, Ruzzoli M. Transcranial stimulation and cognition. *Handb Clin Neurol* 2013;116:739–50.
- [6] Levasseur-Moreau J, Brunelin J, Fecteau S. Non-invasive brain stimulation can induce paradoxical facilitation. Are these neuroenhancements transferable and meaningful to security services? *Front Hum Neurosci* 2013;7:449.
- [7] Krause B, Cohen Kadosh R. Can transcranial electrical stimulation improve learning difficulties in atypical brain development? A future possibility for cognitive training. *Dev Cogn Neurosci* 2013;6:176–94.
- [8] McKinley RA, McIntire L, Bridges N, Goodyear C, Bangera NB, Weisend MP. Acceleration of image analyst training with transcranial direct current stimulation. *Behav Neurosci* 2013;127:936–46.
- [9] McIntire LK, McKinley RA, Goodyear C, Nelson J. A comparison of the effects of transcranial direct current stimulation and caffeine on vigilance and cognitive performance during extended wakefulness. *Brain Stimulat* 2014;7:499–507. doi:10.1016/j.brs.2014.04.008.
- [10] Kwon YH, Kang KW, Son SM, Lee NK. Is effect of transcranial direct current stimulation on visuomotor coordination dependent on task difficulty? *Neural Regen Res* 2015;10:463–6. doi:10.4103/1673-5374.153697.
- [11] Wade S, Hammond G. Anodal transcranial direct current stimulation over premotor cortex facilitates observational learning of a motor sequence. *Eur J Neurosci* 2015. doi:10.1111/ejn.12916.
- [12] Del Felice A, Magalini A, Masiero S. Slow-oscillatory Transcranial Direct Current Stimulation Modulates Memory in Temporal Lobe Epilepsy by Altering Sleep Spindle Generators: A Possible Rehabilitation Tool. *Brain Stimulat* 2015.
- [13] Zhu FF, Yeung AY, Poolton JM, Lee TMC, Leung GKK, Masters RSW. Cathodal Transcranial Direct Current Stimulation Over Left Dorsolateral Prefrontal Cortex Area Promotes Implicit Motor Learning in a Golf Putting Task. *Brain Stimulat* 2015.
- [14] Pisoni A, Turi Z, Raithel A, Ambrus GG, Alekseichuk I, Schacht A, et al. Separating Recognition Processes of Declarative Memory via Anodal tDCS: Boosting Old Item Recognition by Temporal and New Item

Detection by Parietal Stimulation. *PloS One* 2015;10:e0123085.

- [15]Monte-Silva K, Kuo M-F, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimulat* 2013;6:424–32.
- [16]Fricke K, Seeber AA, Thirugnanasambandam N, Paulus W, Nitsche MA, Rothwell JC. Time course of the induction of homeostatic plasticity generated by repeated transcranial direct current stimulation of the human motor cortex. *J Neurophysiol* 2011;105:1141–9.
- [17]Boggio PS, Liguori P, Sultani N, Rezende L, Fecteau S, Fregni F. Cumulative priming effects of cortical stimulation on smoking cue-induced craving. *Neurosci Lett* 2009;463:82–6.
- [18]Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *Br J Psychiatry J Ment Sci* 2012;200:52–9.
- [19]Brunoni AR, Valiengo L, Baccaro A, Zanão TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry* 2013;70:383–91.
- [20]Magis D, Sava S, d' Elia TS, Baschi R, Schoenen J. Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly® device in headache treatment: a survey of 2,313 headache sufferers in the general population. *J Headache Pain* 2013;14:95.
- [21]Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. *Brain Stimulat* 2012;5:155–62.
- [22]Morales-Quezada L, Cosmo C, Carvalho S, Leite J, Castillo-Saavedra L, Rozisky JR, et al. Cognitive effects and autonomic responses to transcranial pulsed current stimulation. *Exp Brain Res* 2015;233:701–9.
- [23]Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull* 2007;72:208–14.
- [24]Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP* 2011;14:1133–45.
- [25]Raimundo RJS, Uribe CE, Brasil-Neto JP. Lack of clinically detectable acute changes on autonomic or thermoregulatory functions in healthy subjects after transcranial direct current stimulation (tDCS). *Brain Stimulat* 2012;5:196–200.
- [26]Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 2003;114:2220–2; author reply 2222–3.
- [27]Russo R, Wallace D, Fitzgerald PB, Cooper NR. Perception of comfort during active and sham transcranial direct current stimulation: a double blind study. *Brain Stimulat* 2013;6:946–51.
- [28]Tadini L, El-Nazer R, Brunoni AR, Williams J, Carvas M, Boggio P, et al. Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents. *J ECT* 2011;27:134–40.
- [29]Bikson M, Datta A, Elwassif M. Establishing safety limits for transcranial direct current stimulation. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 2009;120:1033–4.
- [30]Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimulat* 2012;5:175–95.
- [31]Widdows KC, Davis NJ. Ethical considerations in using brain stimulation to treat eating disorders. *Front Behav Neurosci* 2014;8:351.
- [32]Maslen H, Douglas T, Cohen Kadosh R, Levy N, Savulescu J. The regulation of cognitive enhancement devices: extending the medical model. *J Law Biosci* 2014;1:68–93.
- [33]Fitz NS, Reiner PB. The challenge of crafting policy for do-it-yourself brain stimulation. *J Med Ethics* 2013.
- [34]Peterchev AV, Wagner TA, Miranda PC, Nitsche MA, Paulus W, Lisanby SH, et al. Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. *Brain Stimulation* 2012;5:435–53.
- [35]Minhas P, Bansal V, Patel J, Ho JS, Diaz J, Datta A, et al. Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. *J Neurosci Methods* 2010;190:188–97.
- [36]Shiozawa P, da Silva ME, Raza R, Uchida RR, Cordeiro Q, Fregni F, et al. Safety of repeated transcranial direct current stimulation in impaired skin: a case report. *J ECT* 2013;29:147–8.
- [37]Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. | Biowebspin. Biowebspin Bio-Dashboard Larg Biotech Pharma Medtech Netw n.d. <http://www.biowebspin.com/pubadvanced/article/24713139/> (accessed April 10, 2015).
- [38]Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP* 2011;14:1133–45.
- [39]Harty S, Robertson IH, Miniussi C, Sheehy OC, Devine CA, McCreery S, et al. Transcranial Direct Current Stimulation over Right Dorsolateral Prefrontal Cortex Enhances Error Awareness in Older Age. *J Neurosci* 2014;34:3646–52.
- [40]EEG - Electroencephalography. - Neuromonitoring Blog Dr Richard Vogel n.d.

<http://neurologiclabs.com/home/about-ionm/eeg/>
(accessed April 25, 2015).

- [41] Camel E, O'Connell M, Sage B, Gross M, Maibach H. The effect of saline iontophoresis on skin integrity in human volunteers. I. Methodology and reproducibility. *Fundam Appl Toxicol Off J Soc Toxicol* 1996;32:168–78.
- [42] Draize J, Woodard G, Calvery H. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *JPharmacolExpTher* 1944;8:377–90.
- [43] Guarienti F, Caumo W, Shiozawa P, Cordeiro Q, Boggio PS, Benseñor IM, et al. Reducing Transcranial Direct Current Stimulation-Induced Erythema With Skin Pretreatment: Considerations for Sham-Controlled Clinical Trials. *Neuromodulation J Int Neuromodulation Soc* 2014.
- [44] Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State–Trait Anxiety Inventory (STAI). *Br J Clin Psychol* 1992;31:301–6.
- [45] Analysis of Skewness and Kurtosis | Real Statistics Using Excel n.d. <http://www.real-statistics.com/tests-normality-and-symmetry/analysis-skewness-kurtosis/> (accessed April 18, 2015).
- [46] Glantz SA. *Primer of Biostatistics, Seventh Edition (Primer of Biostatistics. 7 edition. McGraw-Hill Medical; 2011.*
- [47] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. *Brain Stimulat* 2008;1:206–23.
- [48] Richardson JD, Fillmore P, Datta A, Truong D, Bikson M, Fridriksson J. Toward Development of Sham Protocols for High-Definition Transcranial Direct Current Stimulation (HD-tDCS). *NeuroRegulation* 2014;1:62.
- [49] Borckardt JJ, Bikson M, Frohman H, Reeves ST, Datta A, Bansal V, et al. A Pilot Study of the Tolerability and Effects of High-Definition Transcranial Direct Current Stimulation (HD-tDCS) on Pain Perception. *J Pain* 2012;13:112–20.
- [50] Dundas JE, Thickbroom GW, Mastaglia FL. Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 2007;118:1166–70.
- [51] Kronberg G, Bikson M. Electrode assembly design for transcranial Direct Current Stimulation: a FEM modeling study. *Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf* 2012;2012:891–5.
- [52] Highsmith JM, MD. Cervical and Thoracic Spine. *SpineUniverse* n.d. <http://www.spineuniverse.com/anatomy/cervical-thoracic-spine> (accessed April 19, 2015).

FUNDING

Partial funding for this study was provided by a grant to the City College of New York from Thync, Inc., Los Gatos, California, USA.

DISCLOSURE

WJT is a co-founder and equity holding employee of Thync, Inc. WJT is an inventor on pending and issued patents related to methods, systems, and devices for non-invasive neuromodulation. MB holds equity in Soterix Medical, Inc. The City College of New York holds patents on tES with MB and LP as inventors.

Trial Arm	Assessment window	Side Effects	tingling	itching	burning	nauseous	headache	twitching	blurred vision	head pain	forgetfulness	difficulty concentrating	dizziness	difficulty breathing
Sham	Within Session	# Reports (%)	447 (70.2%)	188 (29.5%)	175 (27.7%)	16 (2.5%)	25 (3.9%)	10 (1.6%)	7 (1.1%)	24 (3.8%)	6 (0.9%)	16 (2.5%)	8 (1.3%)	5 (0.8%)
		Avg. Intensity (1-10)	1.80 (±1.7)	0.76 (±1.5)	0.89 (±1.8)	0.05 (±0.5)	0.05 (±0.5)	0.02 (±0.1)	0.01 (±0.2)	0.08 (±0.5)	0.01 (±0.2)	0.06 (±0.5)	0.03 (±0.3)	<0.01
		Avg. Duration (min)	1.20 (±2.3)	0.65 (±1.9)	0.65 (±2.1)	0.12 (±1.4)	0.10 (±1.0)	0.01 (±0.1)	0.01 (±0.2)	0.07 (±0.5)	0.02 (±0.6)	0.24 (±1.9)	0.05 (±0.7)	0 (±0)
	When Reported	Avg. Intensity (1-10)	2.3(±1.6)	2.7(±1.5)	3.4(±2.0)	3.1(±2.0)	4.5(±2.1)	1.1(±0.3)	1.5(±0.8)	2.1(±1.7)	1.6(±1.3)	3.1(±1.9)	2.3(±1.6)	1(±0)
		Avg. Duration (min)	1.7(±2.6)	2.3(±2.9)	2.4(±3.4)	8.7(±9.0)	11.3(±7.9)	1.1(±0.9)	1.8(±2.3)	2.2(±2.1)	5.0(±8.7)	11.5(±7.5)	6.0(±6.5)	0(±0)
	Between Sessions	# Reports (%)	46 (7.3%)	8 (1.3%)	3 (0.5%)	4 (0.6%)	15 (2.4%)	2 (0.3%)	0 (0%)	3 (0.5%)	0 (0%)	2 (0.3%)	1 (0.2%)	1 (0.2%)
tDCS	Within Session	# Reports (%)	357 (57.7%)	191 (30.9%)	144 (23.3%)	4 (0.6%)	27 (4.4%)	8 (1.3%)	17 (2.7%)	17 (2.7%)	7 (1.1%)	29 (4.7%)	9 (1.5%)	3 (0.5%)
		Avg. Intensity (1-10)	1.42 (±2.1)	0.9 (±1.9)	1.02 (±2.4)	0.01 (±0.1)	0.05 (±0.4)	0.01 (±0.1)	0.03 (±0.3)	0.05 (±0.5)	0.02 (±0.2)	0.10 (±0.5)	0.02 (±0.3)	<0.01
		Avg. Duration (min)	4.03 (±6.4)	2.2 (±5.1)	2.07 (±5.1)	0.01 (±0.2)	0.15 (±1.5)	0.01 (±0.1)	0.01 (±0.1)	0.08 (±0.7)	0.06 (±0.9)	0.59 (±3.2)	0.05 (±0.8)	<0.01
	When Reported	Avg. Intensity (1-10)	2.7(±2.2)	3.5(±2.2)	4.8(±2.9)	2.0(±1.4)	3.0(±1.4)	1.0(±0)	3.0(±2.0)	3.8(±2.4)	2.0(±1.3)	2.6(±1.6)	2.4(±1.5)	1(N/A)
		Avg. Duration (min)	8.2(±7.0)	8.2(±6.8)	9.8(±6.9)	3.0(±2.8)	9.7(±7.3)	1.0(±0)	3.2(±3.5)	4.4(±2.7)	6.7(±8.4)	15.3(±6.7)	7.0(±8.8)	1(N/A)
	Between Sessions	# Reports (%)	25 (4.0%)	18 (2.9%)	24 (3.9%)	0 (0%)	8 (1.3%)	0 (0%)	0 (0%)	2 (0.3%)	1 (0.2%)	2 (0.3%)	1 (0.2%)	1 (0.2%)
tPCS	Within Session	# Reports (%)	166 (25.8%)	87 (13.5%)	22 (3.4%)	4 (0.6%)	17 (2.6%)	4 (0.6%)	3 (0.5%)	38 (5.9%)	1 (0.2%)	5 (0.8%)	9 (1.4%)	1 (0.2%)
		Avg. Intensity (1-10)	0.78 (±1.7)	0.40 (±1.3)	0.09 (±0.6)	0.01 (±0.2)	0.06 (±0.5)	0.04 (±0.5)	<0.01	0.16 (±0.7)	<0.01	0.03 (±0.3)	0.03 (±0.3)	<0.01
		Avg. Duration (min)	1.28 (±3.3)	0.72 (±2.6)	0.12 (±1.0)	0.01 (±0.2)	0.06 (±0.7)	0.01 (±0.3)	<0.01	0.31 (±1.8)	0 (±0)	0.05 (±0.8)	0.04 (±0.7)	0 (±0)
	When Reported	Avg. Intensity (1-10)	3.2(±1.9)	3.2(±2.3)	3.1(±1.9)	3.0(±2.8)	2.9(±2.3)	5.8(±4)	1.0(±0)	2.7(±1.4)	1.0(N/A)	3.6(±1.5)	2.5(±2.1)	1(N/A)
		Avg. Duration (min)	5.7(±4.8)	5.9(±5.2)	4.5(±4.5)	3.0(±2.0)	4.0(±4.1)	4.0(±4.2)	2.5(N/A)	5.5(±5.5)	N/A(N/A)	7.3(±8.7)	5.4(±6.7)	0(N/A)
	Between Sessions	# Reports (%)	43 (6.7%)	19 (2.9%)	9 (1.4%)	0 (0%)	8 (1.2%)	1 (0.2%)	0 (0%)	9 (1.4%)	1 (0.2%)	0 (0%)	5 (0.8%)	0 (0%)

Table 1. Summary of side effects incurred within and between sham or tES treatment sessions. All side effect incidences are from self-reported surveys administered daily, before (between session) and after (within session) treatment. Study withdrawal for atypical headache and atypical skin condition was scored automatically as between session headache since subjects did not complete the daily pre-treatment questionnaire the day following the adverse event or adverse reaction.

*Authors contributed equally
#Correspondence: marom.bikson@gmail.com

Group	Number of Sessions	Total Subjects	Finished Trial	Subject that did not meet ongoing inclusion/exclusion criteria					
				Atypical Headache or Migraine		Atypical Skin Condition		Discomfort	
				Between Session	Within Session	Between Session	Within Session	Between Session	Within session
Sham	636	37	33	2	0	2	0	0	0
tDCS	623	33	22	2	0	8	0	0	1
tPCS	646	30	25	3	0	1	0	0	1
Total	1905	100	80	7	0	11	0	0	2

Table 2. Summary of compliance indicated by treatment sessions, study completion and withdrawal rates for sham, tDCS, and tPCS treatment groups. Subjects who did not meet the ongoing inclusion/exclusion criteria were withdrawn for discomfort, atypical headache and atypical skin condition (see Methods). All other subjects we categorized as “finished trial”. Subjects elected how many sessions to complete over 6 weeks with the minimal requirement of completing four treatment sessions per seven days and a minimal enrollment commitment of 2 weeks.

	Δ% Tingling	Δ% Itching	Δ% Burning	Δ% Nauseous	Δ% Headache	Δ% Twitching	Δ% Blurred Vision	Δ% Head Pain	Δ% Forgetfulness	Δ% Difficulty concentrating	Δ% Dizziness	Δ% Difficulty breathing
Sham	18% 7%	46% 1%	6% -0.4%	-0.6% 12.2%	2.6% 10%	-1.6% -0.3%	N/A N/A	2.9% 3.8%	N/A 0%	-2.5% -0.3%	-1.3% -0.2%	-0.8% -0.2%
tDCS	32% 5%	37% 7%	63% 17%	N/A N/A	-4.4% 6.4%	N/A -0.2%	N/A N/A	-2.7% -0.3%	-1.1% -0.2%	45.5% 3.3%	-1.4% -0.2%	-0.5% 0.2%
tPCS	40% 18%	2% 2%	19% 22%	N/A N/A	-2.7% 4.8%	99.5% 25%	N/A N/A	-5.3% 15.3%	-0.2% -0.2%	-0.8% 0.0%	-1.4% 33%	N/A 0%

Table 3: Likelihood for reporting the same adverse events consecutively within (during) and between (post-treatment), as well as between (post-treatment) and within (during the following treatment session) treatments. The likelihood for a subject reporting the same incidence consecutively is shown for all the sessions (sham n = 636, tDCS n = 623, tPCS n = 646). The top delta value shows the percent chance for a subject repeating the reporting of the same adverse event or adverse reaction from within a session to between sessions. The formula used to calculate the delta values shown in the upper quadrants was: (percentage of subjects reporting a within session adverse and the same adverse event between sessions) – (percentage of subjects not reporting a within session adverse event, but reporting a between session adverse event). The delta value shown in the bottom quadrant indicates the percent chance for a subject experiencing the same adverse event from between a session to the next within session. The formula used to calculate the delta value shown in the bottom quadrant was: (percentage of subjects reporting an adverse event between sessions and the same adverse event during the next within session period) – (percentage of subjects who did not report an adverse event between a session, but who reported an adverse event during the next within session period). The within to between session values were high for skin tingling (tDCS = 32%, tPCS = 40%), skin itching (sham = 46%, tDCS = 37%) and mild burning sensations (tDCS = 63%) indicating the likelihood of subjects reporting the same incidence consecutively. However high values for twitching (tPCS = 99.5%), dizziness (tPCS = 33%), and difficulty concentrating (tDCS = 45.5%) cannot be deemed reliable due to small percent of reports for twitching (tPCS = 0.6%), dizziness (tPCS = 1.4%), and difficulty concentrating (tDCS = 4.7%).



Figure 1. Study space used as a dedicated “stimulation lounge” for the naturalistic environment in the study. The lounge where the treatment sessions were conducted is shown. The naturalistic space was intended to be a relaxing, lounge-like location where subjects sit quietly and conduct normal activities while receiving treatment. Both a sofa area and desk area (now shown) were available to subjects and Wi-Fi access was provided so subjects could browse the internet, listen to music, or converse quietly amongst each other.

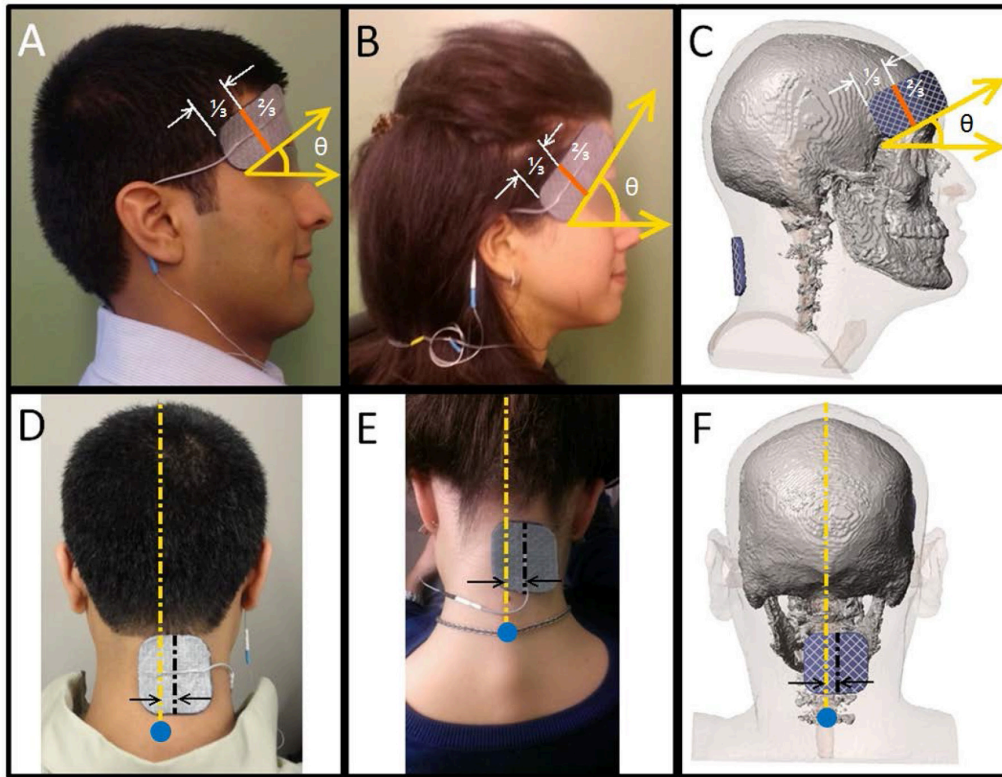


Figure 2. Electrode configurations and montages. Identical electrodes and montages were used across all treatment arms to allow for testing of the influence of variable waveforms on safety and tolerability. The rectangular anode electrode was placed on the subjects' right temples after asking them to bite down for reference (panels A, B, C). The third of the electrode (landscape orientation reference) which is closest to the side at which the wire exits was placed over the temple. The other two thirds of the electrode was balanced towards the forehead at about a 45 degree angle (plane parallel to the floor reference shown by panel A, B, C) while avoiding as much of the subjects' hairline as possible. As shown in panels D, E, F, the middle of square cathode electrode (dashed black line) was placed about 1 cm to the right of the subjects' midline (vertical dashed yellow line) on the back of the neck. The electrode was placed above the cervical spine vertebrae C7 which is marked with blue circle in panels D, E, F. The C7 bone is the last bone on the cervical vertebrae and generally protrudes, especially when bending the neck [52]. As needed, medical tape was used to ensure the edges of the cathode made good contact with the skin.

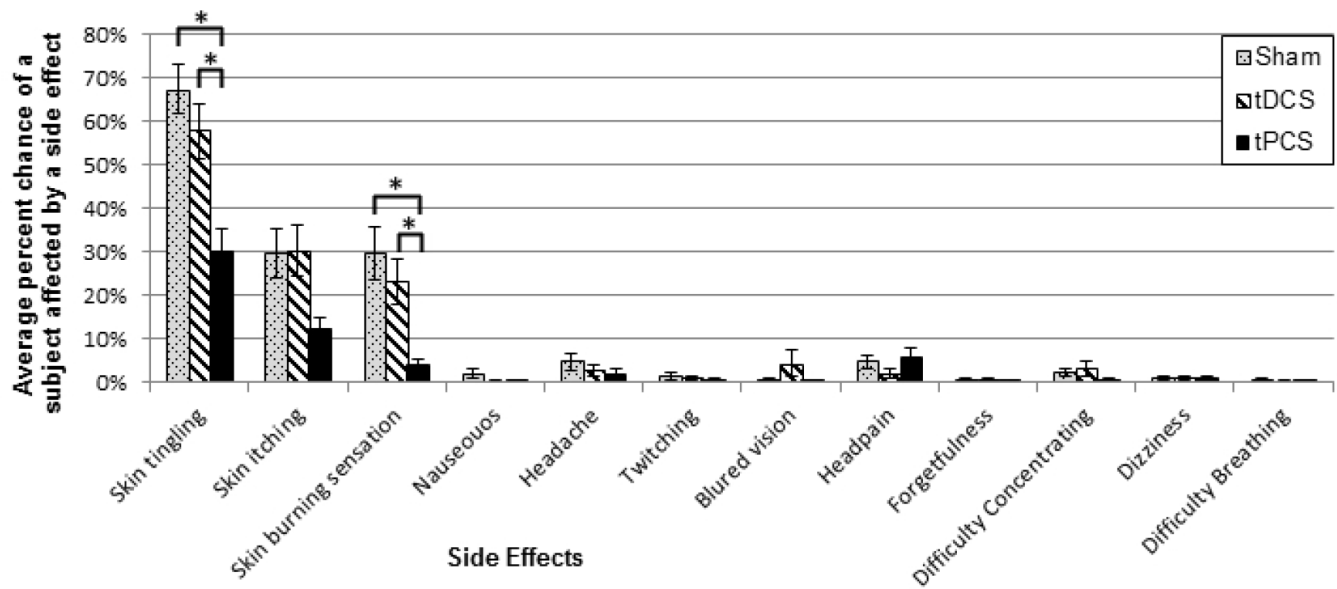


Figure 3. Percent chance of reporting side effect for each subject: The average percent chance for a subject $n = 37$ Sham 33 tDCS, and 30 tPCS affected by a side effect within session. The percent is derived by calculating the total number of sessions a side effect was reported by a subject from the total number of sessions completed by the subject. The rate of reporting skin tingling for tPCS was lower than sham ($p = 9 \times 10^{-5}$) and tDCS ($p = 0.005$). Furthermore, the rate of reporting skin burning sensation in tPCS was also lower than Sham ($p = 0.006$) and tDCS ($p = 0.003$). The error bars show the standard error of the mean. An asterisk indicates $p < 0.01$.

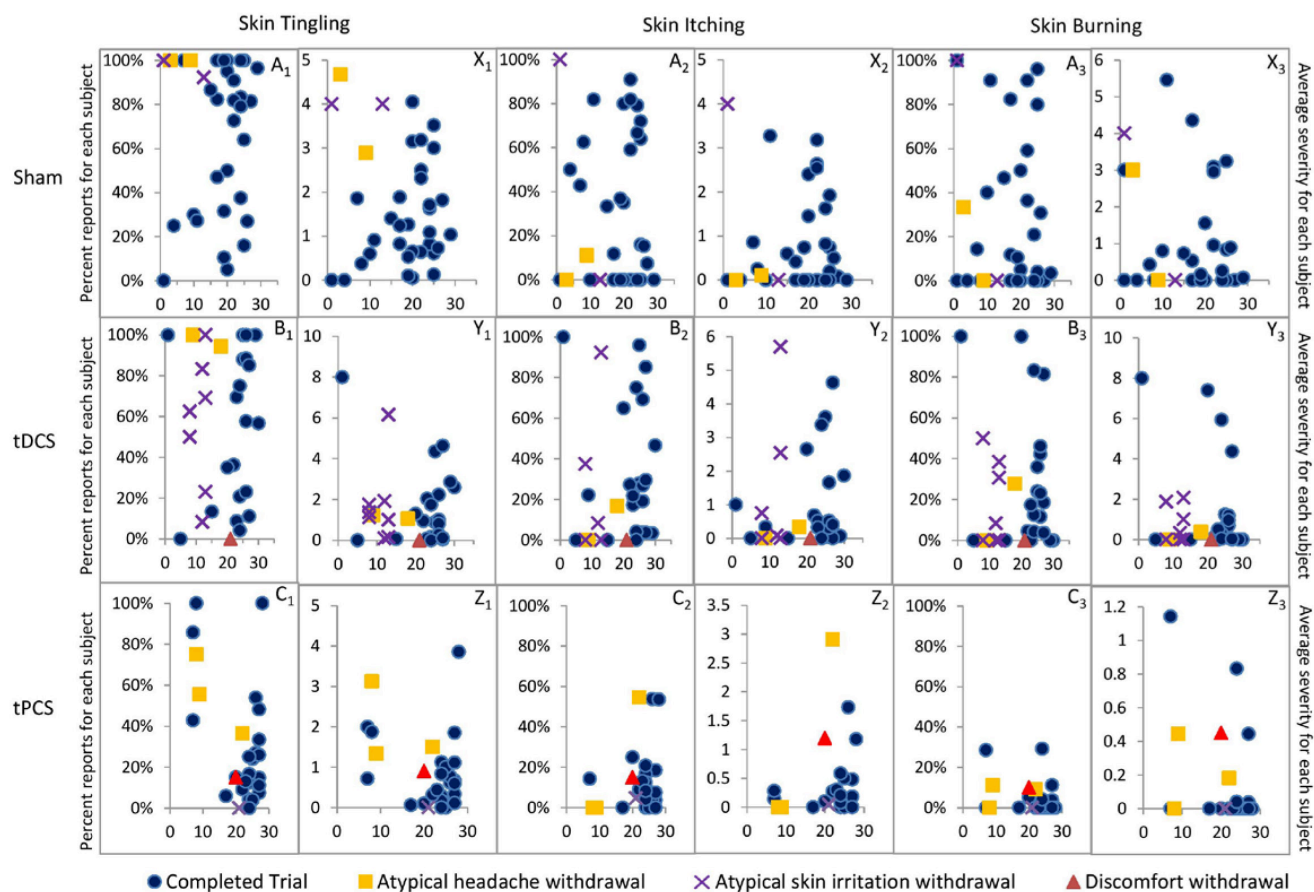


Figure 4. Side effect incidence and severity does not affect compliance of individual subjects. The occurrence of common side effects (skin tingling = A₁-C₁, skin itching = A₂-C₂, and skin burning sensation = A₃-C₃) is plotted as a percentage against the total number of treatment sessions completed for each subject by experimental groups (sham n = 37, tDCS n = 33, and tPCS n = 30). There was no correlation between percentage of side effects reported by subjects and the total number of treatment sessions they completed. The average severity of side effects (skin tingling = X₁-Z₁, skin itching = X₂-Z₂, and skin burning sensation = X₃-Z₃) is plotted against the number of sessions completed by each subject. There was no correlation between average side effect severity and the total sessions completed. Subject withdrawals for atypical headache, atypical skin irritation, and discomfort are indicated by the symbols purple X, yellow-square, and red-triangle respectively. Since only a few subjects withdrew due to atypical headache, atypical skin condition, or discomfort in sham, tDCS, and tPCS treatment groups, no trends can be inferred based on severity, incidence, or total sessions completed.

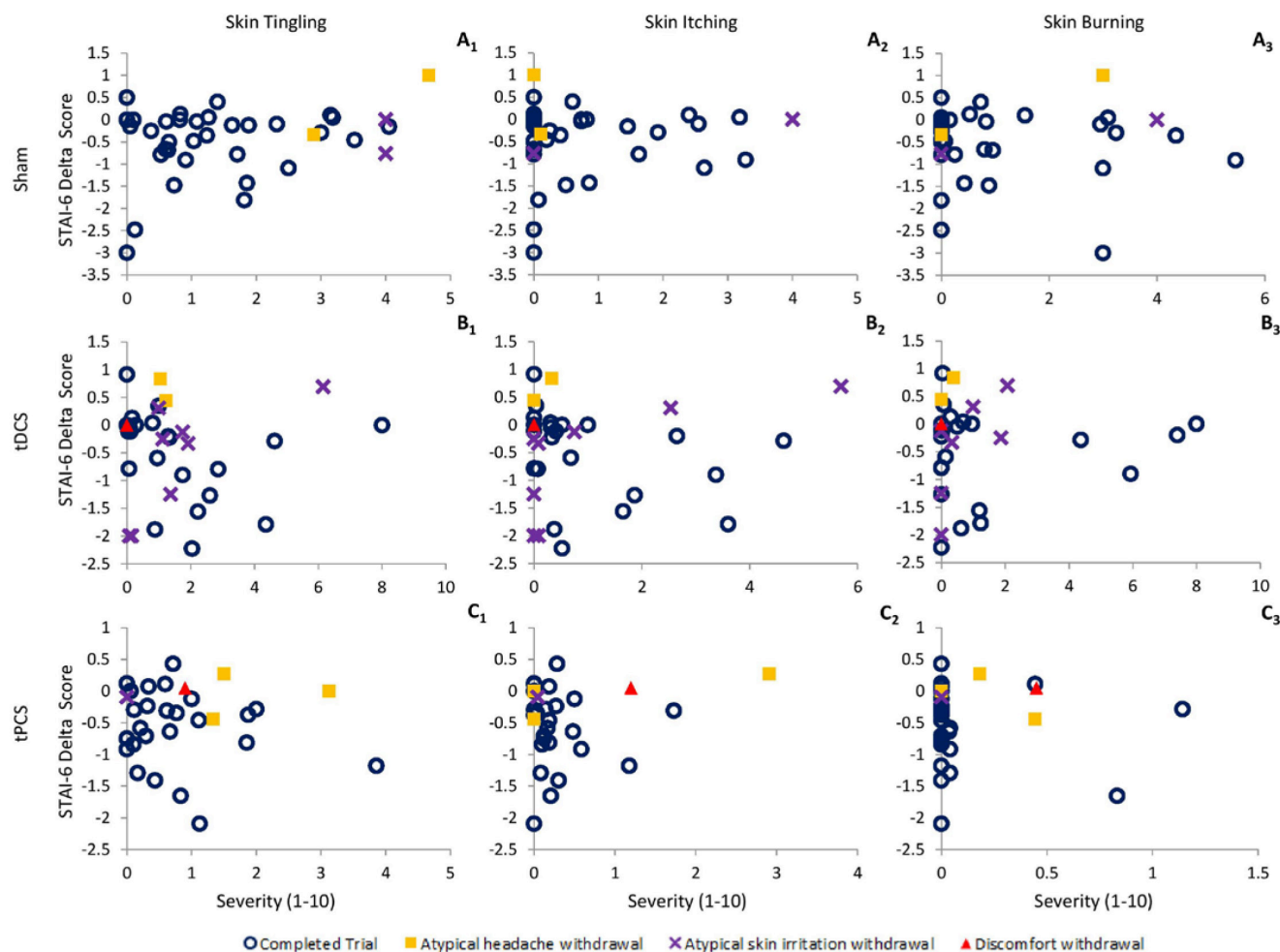


Figure 5. Side effect severity did not affect state anxiety levels as indicated by STAI-6 delta scores. The STAI-6 delta score (y-axis) reflects state anxiety changes and is plotted for each subject (sham $n = 37$, tDCS $n = 33$, and tPCS = 30) against side effect (skin tingling = A₁-C₁, skin itching = A₂-C₂, and skin burning sensation = A₃-C₃) severity (x-axis) by treatment groups. Subject withdrawal for atypical headache, atypical skin irritation, and discomfort are indicated by a purple X, yellow-square, and red-triangle respectively. There was no significant trend between STAI-6 delta scores and side effect severity within treatment groups for skin tingling, itching, and burning sensations. Since the number of subjects withdrawing from the trial is small, no trends could be identified between withdrawal reason/severity and STAI-6 delta scores.

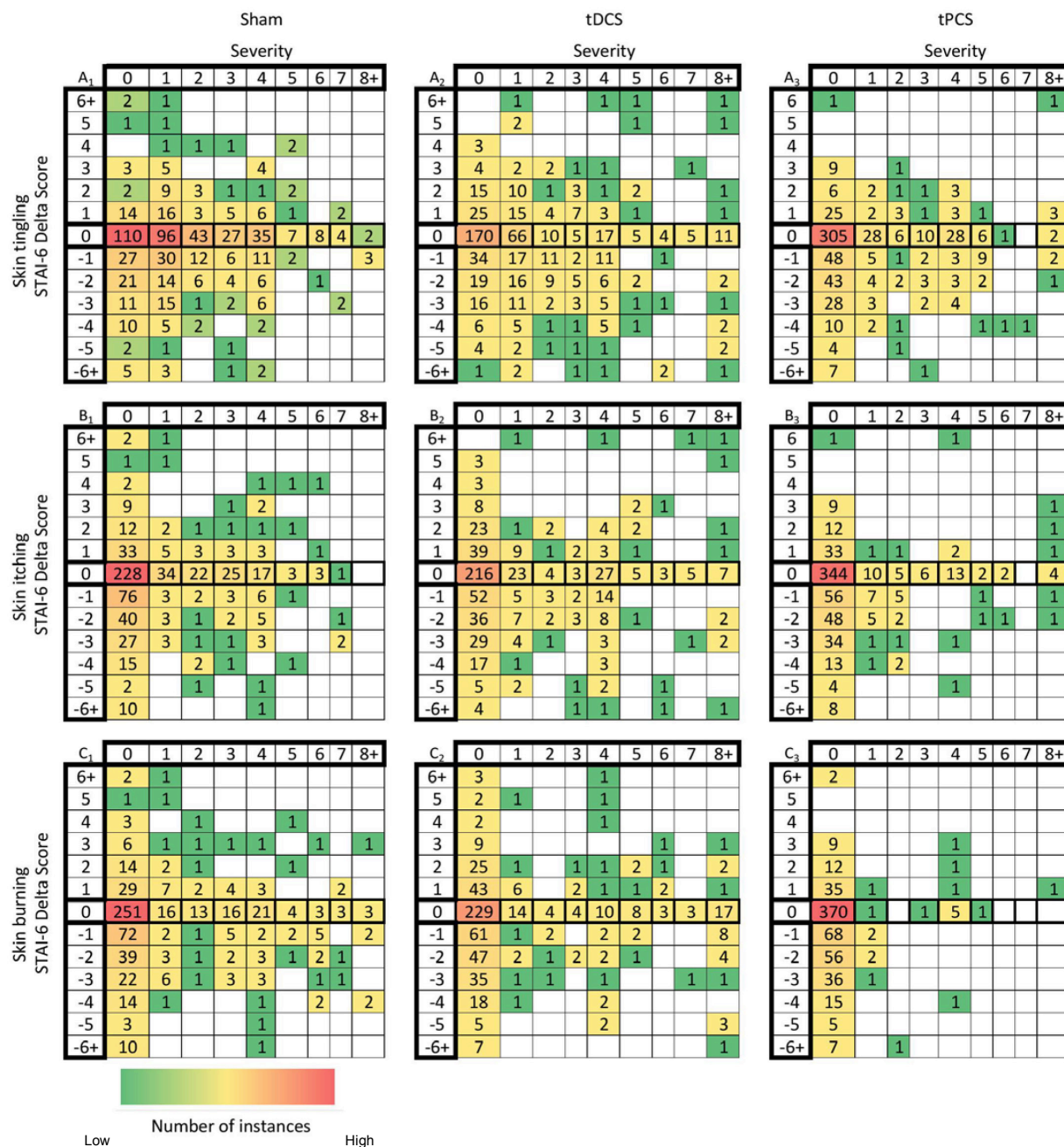


Figure 6. Relationship between state anxiety (STAI-6 delta scores) and adverse event severity by treatment sessions. The heat-map grids shows the number of adverse event instances by session (sham $n = 636$, tDCS $n = 623$, and tPCS $n = 646$) for each STAI-6 delta score corresponding to the reported severities for skin tingling (A₁-A₃), itching (B₁-B₃), and mild skin burning sensations (C₁-C₃). The STAI-6 delta score shows the overall stress level for each subject and is calculated based on 6 questions in both pre- and post-treatment questionnaires. There are high instances along zero severity and along zero STAI-6 delta scores since the majority of subjects did not experience a change in state anxiety levels or report a side effect after treatment. A few data points fell above a severity of 8 and a STAI-6 delta score of -6 or 6 and these data points are indicated in the columns or rows labeled with 8+, -6+ and 6+ respectively. No evident relationship was found between state anxiety (STAI-6 delta scores) and adverse event severity across the treatment sessions.

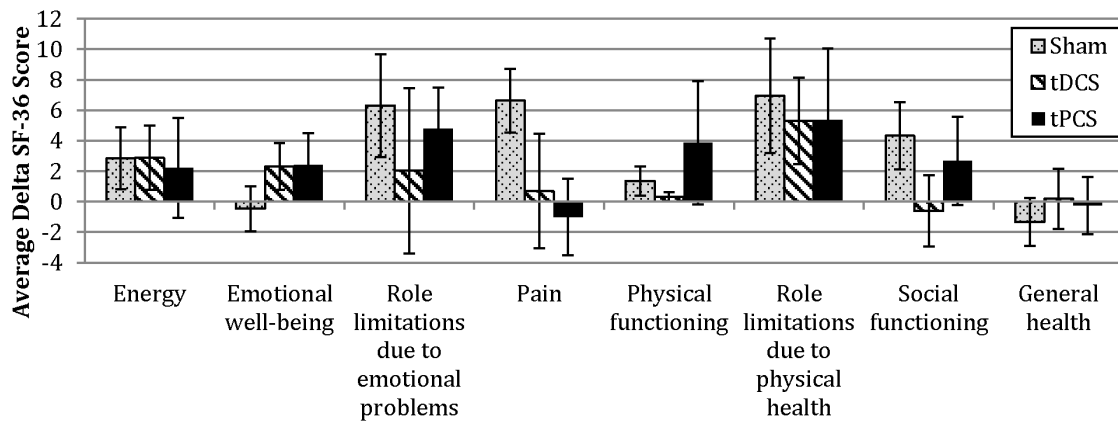


Figure 7. Repeated use of tES had no significant detriment on quality of life as indicated by the SF-36 Health Survey. The change in scores (delta) obtained from the SF-36 administered before the first treatment session of the trial and at the end of the last treatment session of the trial are represented by histograms. The 36 questions in SF-36 Health Survey fall in to the eight categories: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Each question is scored on a scale of 0 to 100. For each of the questions and categories, a higher score defines a more favorable health state. The figure shows the average delta scores between the first and last session for subjects (Sham n = 37, tDCS n = 33 and tPCS n = 30). There was no significant differences found across the three treatment groups on any of the eight quality of life categories indicating that repeated use of tES had no significant detriment on the quality of life reflected by the SF-36 questions. The error bars indicate the standard error of the mean.

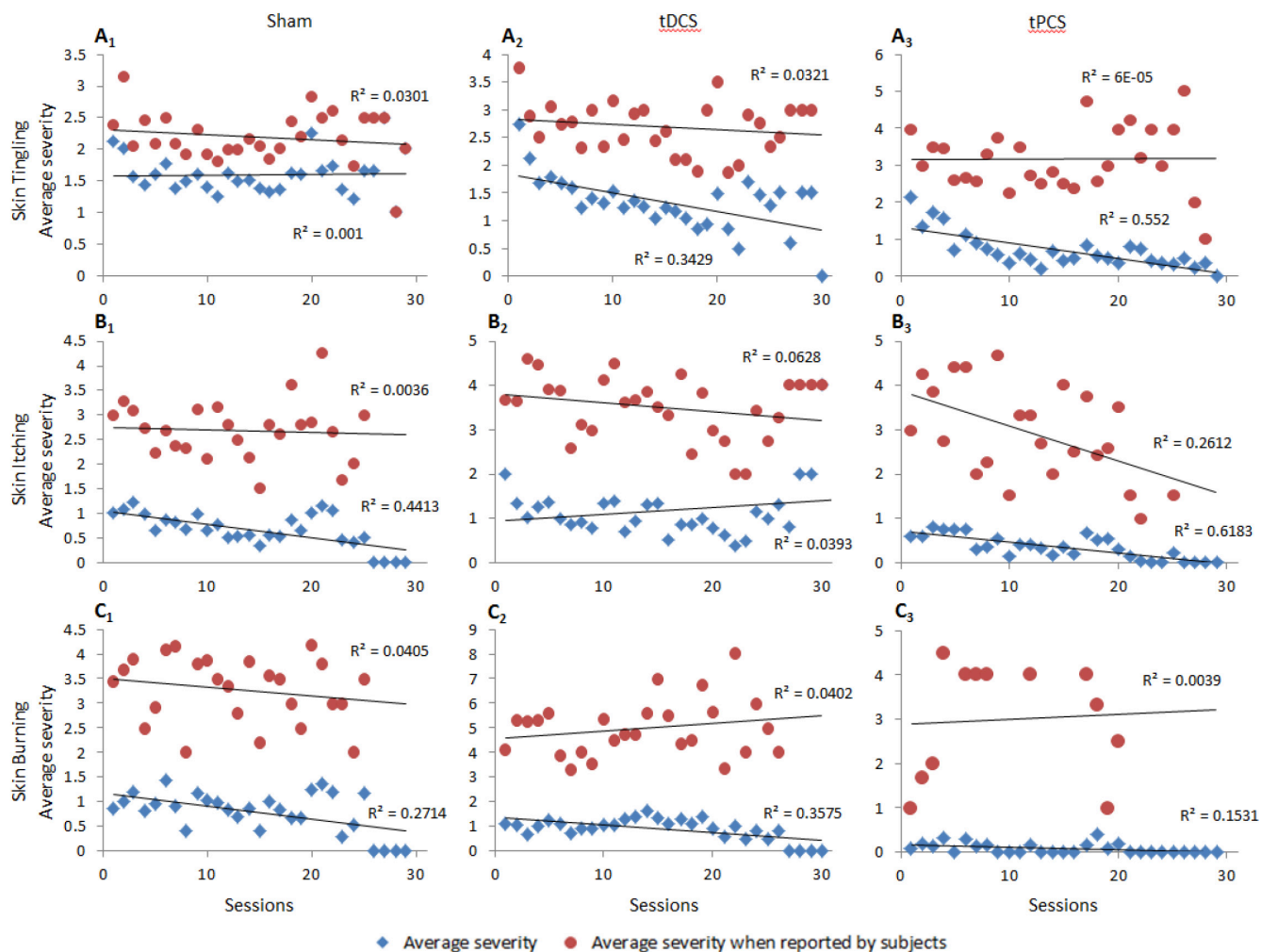


Figure 8. Average adverse reaction severity remains stable or tends to decrease across treatment sessions. The average severities of common adverse reactions are plotted across the 30 treatment sessions for skin tingling (A₁-A₃), skin itching (B₁-B₃) and mild burning sensations (C₁-C₃) by treatment group. The average severity when an adverse reaction was reported by subjects (red circle) is higher and shows high variability compared to the grand average severity (blue diamonds) since the severity was assumed to be zero when an adverse reaction was not reported by subjects. Overall there was a general trend of decreasing average adverse reaction severity across the 30 treatment sessions as shown in panels A₂, A₃, B₁, B₃, C₁, and C₂.