Tolerability and blinding of 4x1 high-definition transcranial direct current stimulation (HD-tDCS) at two and three milliamps

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Abstract

Background: Transcranial direct current stimulation (tDCS) is an in-demand form of neuromodulation generally regarded as safe and well tolerated. However, few studies have examined the safety, tolerability, or blinding of High Definition (HD-) tDCS, especially in older adults and at stimulation intensities of 2 milliamps (mA) or greater.

Objective: We examined the rates of serious adverse events and common side effects to establish safety and tolerability, respectively, in HD-tDCS. Blinding was evaluated using participants’ accuracy in correctly stating their condition (i.e., active or sham).

Methods: The sample included 101 older adults (Mage = 69.69, SD = 8.33; Meduc = 16.27, SD = 2.42) who participated in our double blind randomized controlled studies or in case studies that used HD-tDCS for 20–30 min at 2 mA (n = 66, 31 active) or 3 mA (n = 35, 20 active). Participants completed a standardized side effect questionnaire and were asked whether they received active or sham stimulation at the end of each session.

Results: There were no serious adverse events and no participants withdrew, suggesting that HD-tDCS meets basic safety parameters. Tolerability was comparable between active and sham HD-tDCS regardless of intensity (2 mA and 3 mA) in first session (all p > .09). Tingling was the most commonly endorsed item (59% active; 56% sham) followed by burning sensation (51% active; 50% sham), the majority of which were mild in nature. “Severe” ratings were reported in fewer than 4% of sessions. Blinding appeared adequate since there were no significant group differences between individuals correctly stating their stimulation condition ($\chi^2 = 0.689, p = .679$). The above tolerability and blinding findings generally persisted when multiple session data (i.e., 186 total sessions) were considered.

Conclusions: HD-tDCS appears well-tolerated and safe with effective sham-control in older adults, even at 3 mA. These data support the use of HD-tDCS in randomized controlled trials and clinical translation efforts.

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Evidence suggests that traditional pad-based tDCS is generally well-tolerated [1–3] with well-documented sensory side effects that include itching, tingling, headache, and burning sensation [1]. Empirical findings suggest similar side effect profiles between active and sham tDCS [1,4], though some of these sensations (e.g., tingling, itching) may be more often reported during active sessions [5]. An important caveat is that roughly 96% of tDCS sessions to date have been limited to 2 mA or lower [6]. Within this range, one study reported increasing discomfort as intensity increased from 0.75 mA to 2 mA [7], whereas another study found no significant discomfort in intensities of 1, 2, 2.5, 3, 3.5 or 4 mA in patients who experienced a stroke [8]. Given the current study’s focus on aging, it is relevant to note that older adults report significantly fewer side effects relative to younger adults [9] and appear less likely to report side effects with increasing age [5]. A comprehensive review of over 33,000 sessions found no evidence of serious adverse events [5], reinforcing the safety profile of tDCS. Blinding generally appears effective as participants have not been able to correctly judge their condition (i.e., active or sham) at better than chance level [10,20], suggesting effective blinding at least under some conditions. At chance levels [10,20], suggesting effective blinding at least under some conditions.

Methods

Participants

One-hundred-one participants who had taken part in IRB-approved studies completed a total of 287 sessions (all studies were listed on clinicaltrials.gov; NCT02155946; NCT01958437; NCT02442843; NCT03034954; NCT03036319). All participants were recruited from the University of Michigan Alzheimer’s Disease Center, the University of Michigan Health Research website, Emory University, VA Ann Arbor Healthcare System, or the Atlanta Veterans Affairs Medical Center.

Basic characteristics of the stimulation naïve (i.e., first HD-tDCS session) sample are included in Table 1. Diagnostic groups included cognitively intact individuals (n = 63), those with mild cognitive impairment (MCI; n = 33), posttraumatic stress disorder (n = 1), primary progressive aphasia (PPA; n = 4), and post-anoxic leukencephalopathy (n = 1). All participants completed a brief neuropsychological evaluation or global screening measure at the time of enrollment in order to establish their cognitive phenotype. Participants were considered cognitively intact if performances were within normal limits (i.e., within 1 standard deviation of the mean) relative to demographically comparable normative data. MCI diagnosis followed the Albert et al. [21] criteria that require 1) subjective report of cognitive decline (self or informant), 2) objective evidence of decline, and 3) generally intact everyday functioning. The participant with PTSD (drawn from NCT02442843) met DSM-IV diagnostic criteria at the time of participation. The participants with PPA met criteria established by the National Alzheimer’s Coordinating Center (NACC [22]).

**HD-tDCS methods**

All studies used a Soterix Medical Inc. Clinical Trial or 1 × 1 TES unit with attached HD-tDCS (4 × 1) adapter. As is standard, electrodes have a four millimeter radius and were configured with a center electrode and four surrounding “ring” electrodes that varied based on study specific montages (provided below). Current density under the center electrodes ranged from 0.44 mA/cm² (for 2 mA) to 0.6 mA/cm² (3 mA), while ring electrodes ranged from 0.11 mA/cm² to 0.15 mA/cm² (assuming an equal passive split). All active conditions consisted of a 30-s ramp up, the assigned intensity and duration of stimulation, and then a 30-s ramp down period. Sham conditions used a 30-s ramp up to the appropriate intensity, followed immediately by a 30-s ramp down; this ramp up-down was performed at the beginning and end of the session in order to control for primacy and recency effects.

Study 1 (n = 9 with first-session data; multi-session data were included for 7 additional participants co-enrolled with Study 2; NCT02155946 [23]) performed HD-tDCS at 2 mA for 30 min over the left lateral prefrontal cortex (center anode at F5; ring electrodes at F1, F3, F5, C5). Study 2 (NCT01958437) performed HD-tDCS at 2 mA for 20 min over superior parietal cortex either bilaterally (center electrode at Pz, ring electrodes at Pz, Oz, P7, P8; n = 12 with first and multi-session data) or over the right hemisphere (center anode at P2, ring electrodes at Cp2, Pz, P6, PO8; n = 43 with first and multi-session data). Study 3 (n = 1 with 10 sessions); NCT02442843 [24] targeted the right lateral temporal cortex (center cathode over T8, ring electrodes at F8, C4, P8, EX10) using 2 mA for 20 min. Study 4 (NCT03036319) consisted of case-specific protocols: 1) (n = 1 with 28 sessions) HD-tDCS performed at 2 mA for 20 min over the left lateral prefrontal cortex (same montage as

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive statistics for baseline characteristics for unique individuals (n = 101).</th>
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<tbody>
<tr>
<td></td>
<td>Sham (n = 50)</td>
</tr>
<tr>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>69.80</td>
</tr>
<tr>
<td>Education</td>
<td>16.40</td>
</tr>
</tbody>
</table>

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in Study 1), 2) \( (n = 1 \text{ with 10 sessions}) \) HD-tDCS performed at 3 mA for 20 min over left lateral temporal cortex (center anode over T7, ring electrodes at F7, C3, P7, EX9), and 3) \( n = 3 \text{ with 3 mA for 20 min (center anode over FT7, ring electrodes at AF7, FC3, TP7, EX11)}. \) Study 5 (\( n = 31; \text{NCT0304954}) \) performed HD-tDCS at 3 mA for 20 min over the left lateral prefrontal cortex using the same montage as in Studies 1 and 4. Studies 1, 2, and 5 used a randomized, double-blind approach, which was not possible with the case studies (i.e., #3 & 4).

Those studies using the Clinical Trial unit (Studies 1, 2, 3) utilized a participant-specific code that was entered into the unit at the start of the session that engaged a pre-programmed condition (i.e., active vs. sham for appropriate intensity and duration), thereby ensuring study team members were blind to stimulation condition. Studies 4 and 5 used TES units. During study 5, one study team member performed stimulation while a different member, blinded from the stimulation type, collected the behavioral outcome measures (not reported here), side effect questionnaires, and blinding data. Thus, all non-case studies used double-blind methodology. Only Study 1 was ongoing at the time the data were extracted, which was done for a report to our institutional review board. We ensured that study staff remained blinded to this process so as not to introduce any bias.

**Tolerability and blinding**

Immediately following stimulation, participants completed an adapted form of the side-effect questionnaire developed by Brunoni and colleagues [2]. This questionnaire consists of ten commonly-reported side effects (i.e., headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, and acute mood changes) as well as an “other” category that allows participants to describe experiences/sensations not otherwise covered. The verbally administered questionnaire asks participants to rate the intensity of side effects (i.e., 0 = absent; 1 = mild; 2 = moderate; 3 = severe). Although the standard questionnaire also asks participants to rate his or her perception of how related each endorsed side effect is to tDCS, we omitted these data given our focus on the experience/intensity of the side effects and because we have generally found participants tend to attribute all side effects to stimulation. Protocols required study team members to immediately alert the senior author (BMH) to any serious adverse events, none were reported by participants or study team members to immediately alert the senior author (BMH) to any serious adverse events, none were reported by participants or study team members to immediately alert the senior author (BMH).

To ensure our findings were not biased by any individual study, we performed the above analyses within Studies 1, 2, and 5 individually (case studies were excluded). Results were unchanged for single session data and nominally changed for multi-session data. These additional findings are provided as Supplemental Materials.

**Results**

Baseline demographics are provided in Table 1. First session data for the 101 participants were composed of 66 participants with 2 mA (Active \( n = 31, \text{Sham} n = 35 \)) and 35 with 3 mA (Active \( n = 20, \text{Sham} n = 15 \)).

**Objective 1: tolerability & safety**

The frequency with which each of the side effects was reported in the first stimulation session, when all participants were HD-tDCS naive, is shown in Table 2. Responses for the ‘Other’ side effect were missing for four individuals (\( n = 97 \)); all other side effects were rated by all 101 participants. Burning, itching, and tingling sensations were relatively commonly reported for both active and sham conditions, while side effects such as headache, neck pain, scalp pain, skin redness, sleepiness, concentration changes, and mood changes were uncommonly endorsed. Severely rated side effects were rare: scalp pain, tingling, and burning were described as “severe” in 4% or fewer of the sessions. “Other” sensations included feeling the gel contact with the head, a “pinprick,” “prickling,” “piercing,” “twitch” or “pooring” sensation, a feeling of “warmth” or “chilling” at electrode sites, “anxiety,” or a feeling of being “floaty” or “light-headed.” Rarely, individuals reported localized tingling in other areas of the body, including “left big toe” and “left hand ring and little finger.” One participant reported smelling burning hair but did not provide a severity rating and did not attribute it to stimulation.

There were no significant differences between active and sham groups in the report of any side effect across the entire sample (i.e., 2 mA and 3 mA combined; Table 2; all \( p > .05 \)). There were no significant differences between active and sham in side effect profile when 2 mA and 3 mA were compared separately (Table 3; \( p > .05 \)).

**Objective 2: blinding**

Case studies were removed from blinding analyses because they did not occur in a randomized, double-blind manner, resulting in a sample of 95 individuals (Active \( n = 46, \text{Sham} n = 49 \)). Chi-squared tests revealed that active and sham groups did not differ in their ability to accurately judge whether they received active or sham stimulation after the first stimulation session (\( \chi^2 = 0.689, p = .679; \) Table 4). We repeated these contrasts for those receiving 2 mA (Active \( n = 30, \text{Sham} n = 34 \)) and 3 mA (Active \( n = 16, \text{Sham} n = 15 \)) separately and found no significant differences in ability to correctly judge condition at 2 mA (active vs. sham: \( \chi^2 = 0.618, p = .764 \)) or at 3 mA (\( \chi^2 = 4.684, p = .113 \)).

We completed exploratory analyses on these single session data to examine whether sex affected the rates of side effects. We found that a greater proportion of women reported the presence of tingling, while a greater proportion of men reported the presence of mild itching. Importantly, however, there were no differences within each sex when these side effects were compared between active and sham side (Supplemental Materials, Table 4).

**Exploratory analyses**

To ensure our findings were not biased by any individual study, we performed the above analyses within Studies 1, 2, and 5 individually (case studies were excluded). Results were unchanged for single session data and nominally changed for multi-session data. These additional findings are provided as Supplemental Materials.
aggregated data, thereby supporting the combined data approach. Excluding those with only single stimulation naïve session data yielded 65 individuals who completed a total of 186 sessions. Across these sessions, (73 sham [70 at 2 mA, 3 at 3 mA] and 113 active [104 at 2 mA, 9 at 3 mA]; Table 5). Only sleepiness differed between the groups \( (\chi^2 = 0.083, p = .936) \), with more active than sham participants reporting this effect (particularly at the “mild” level). However, this difference in sleepiness appeared to vary across the individual studies with nominal (Study 2) differences or greater report in sham than active (Study 1). Consistent with single-session findings, burning, tingling, and itching sensations were fairly commonly reported by participants in both groups. “Severely” rated side effects were endorsed in only 1–3% of the sessions (Table 5). No serious adverse events were reported or observed and 100% of participants completed all tDCS sessions.

Blinding data were available from 141 sessions (active sessions = 72, sham sessions = 69; sessions from case studies were removed). Significant differences were evident in the frequency of judged stimulation condition \( (\chi^2 = 11.820, p = .003; \text{Table 6}) \); a difference that was driven by a higher proportion of participants in the sham group believing they received active stimulation relative to those actually receiving active HD-tDCS.

**Discussion**

The present report is the largest to date examining tolerability, aspects of safety, and blinding in stimulation naïve older adults who underwent 2 mA and 3 mA HD-tDCS. Our findings complement safety and tolerability profiles of traditional pad-based tDCS [3,6]. While we discuss tolerability and blinding below, the absence...
of any serious adverse events in over 280 sessions with 101 older adults reinforces recent findings from pad-based tDCS [3,6] and suggests that HD-tDCS meets basic safety standards. However, it should be noted that “safety” is defined in very limited terms (i.e., no serious adverse events), so the scope may need to be refined to better understand any adverse effects/events of HD-tDCS, especially in the long-term.

Tolerability is a critical factor to consider when providing any type of intervention. Prior reviews of pad-based tDCS, found that itching (32.9–39% of sessions) and tingling (18.3–22% of sessions) are the most commonly experienced sensations [2,25]. Our first-session HD-tDCS data found that tingling (59%) and burning sensation (51%) were the most commonly reported side effects in those receiving active stimulation whereas itching was only reported in 24% of sessions. These rates were comparable to those experienced by the sham group (e.g., tingling = 56%, burning sensation = 50%, itching = 20%). Thus, there may be some relative differences between pad-based and HD-tDCS that presumably reflects the size and distance between the electrodes (and hence the current density) as well as the preparation of the electrodes. Likewise, skin redness was previously discussed as a factor that may interfere with blinding [13], which is why we evaluated it after completing all other post-stimulation questionnaires. We found low rates of redness in our combined data (0% in active; 6% in sham). Such rates are likely related to a number of factors including the noted delay, use of gel rather than saline, and smaller skin surface area under the electrode. Similar procedures could be implemented in future trials to mitigate bias arising from detection of skin redness.

The majority of the side effects (96–98%) were rated as mild or moderate, regardless of whether participants received active or sham HD-tDCS. Severe ratings were provided in a maximum of 7% of 3 mA sham sessions (note the rate was lower in active sessions). These findings generally persisted when we evaluated 186 subsequent sessions (i.e., multisession data that excluded first session), where only the rate of (mild) sleepiness differed between active and sham HD-tDCS. The comparable profiles in the active and sham sessions at 3 mA suggest that higher intensities can be more thoroughly investigated using HD-tDCS.

The comparable side effect profiles suggest that sham HD-tDCS elicits sensory experiences indistinguishable from those of active stimulation. Although some subtle differences may emerge across multiple sessions (i.e., sleepiness), it seems unlikely that sleepiness would be a risk to blinding or tolerability at the individual participant level. Regardless, the data revealed that participants were equally likely to believe they received active stimulation regardless of whether they experienced active or sham stimulation. Our findings support other HD-tDCS reports [10] and argue against concerns that higher intensities will compromise blinding [13]. Such findings are critical for clinical trial design given the ability to control for perceptual experiences. However, clinical translation requires the use of multiple sessions but this may inadvertently allow the participant to reflect back on prior experiences and more accurately determine their stimulation condition [9,26,27], especially if a cross-over design is used [28]. While significant differences in the frequency of the stated condition emerged from the multi-session data, they appeared due to a higher percentage of sham participants reporting that they received “active” stimulation. These results suggest that blinding can not only be maintained with multiple HD-tDCS sessions but that participants may become increasingly likely to believe they are receiving active stimulation across additional sessions. However, a parallel groups design will likely be especially appropriate as the length of intervention with (HD-) tDCS increases due to the potential cumulative experience. Although we did not evaluate study team blinding, future studies should consider doing so to ensure effective double-blind procedures.

Exploratory analyses raised the possibility of sex-specific differences in side effect profile with males reporting more itching but females reporting more tingling. Given the absence of difference between active and sham within each sex for these particular side effects, it seems unlikely that these findings hold any particular significance for tolerability or blinding. Regardless, future studies should be aware of, and monitor for, such differences.

Limitations of the current study include challenges that arise from combining data across different studies/montages, though this affects any efforts to combine data across studies (e.g., tolerability data in Refs. [2,3]). It is unlikely that the current findings were biased by any particular study given the highly consistent patterns that were observed within each individual dataset via exploratory analyses. Statistical power may have been limited by the low endorsement rates for some side effects; however, such reports presumably reflect the underlying population level base rate occurrences and represent “rare” effects. More data are needed at higher intensities (e.g., 3 mA) in order to verify the current findings so caution is warranted when extrapolating beyond the current

### Table 5
Frequency of endorsement (%) of side effects endorsed during multiple Active (Sessions — 113; 104 at 2 mA, 9 at 3 mA) and Sham (Sessions — 73; 70 at 2 mA, 3 at 3 mA) Sessions from 65 participants.

<table>
<thead>
<tr>
<th></th>
<th>None Active</th>
<th>None Sham</th>
<th>Mild Active</th>
<th>Mild Sham</th>
<th>Moderate Active</th>
<th>Moderate Sham</th>
<th>Severe Active</th>
<th>Severe Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>97</td>
<td>97</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>98</td>
<td>99</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Scalp Pain</td>
<td>90</td>
<td>85</td>
<td>8</td>
<td>8</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tingling</td>
<td>42</td>
<td>34</td>
<td>48</td>
<td>55</td>
<td>8</td>
<td>10</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Itching</td>
<td>61</td>
<td>63</td>
<td>35</td>
<td>30</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Burning</td>
<td>51</td>
<td>41</td>
<td>35</td>
<td>40</td>
<td>12</td>
<td>16</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Skin Redness</td>
<td>96</td>
<td>97</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>79</td>
<td>90</td>
<td>18</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Concentration Changes</td>
<td>88</td>
<td>93</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mood Changes</td>
<td>96</td>
<td>96</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Other Symptoms</td>
<td>94</td>
<td>95</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: ‘Other Symptoms’ missing data for 3 sessions; ‘Skin Redness’ missing data for 1 session; Bold and * indicates statistically significant at p < .05.

### Table 6
Group estimation in multiple HD-tDCS sessions (n = 62, Active Sessions — 72, Sham Sessions — 69).

<table>
<thead>
<tr>
<th></th>
<th>Said Sham</th>
<th>Said Active</th>
<th>Said DK</th>
<th>$\chi^2$</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
</table>
| Sham           | 16         | 72          | 12      | 11.820   | 2  | .003*
| Active         | 38         | 44          | 18      |          |    |      |

Note. DK = “Don’t Know”; Bold and * indicates statistically significant at p < .05.
population and methodology. Likewise, the effects of cross-over designs should be further evaluated since within-versus between-subject differences may differ.

Accurate side effect measurement is vital for inter-study validity. While a much-needed advance in the field, experience working with HD-tDCS revealed some limitations of the existing side effect questionnaire [2]. First, it does not evaluate side effects that could be associated with mere electrode placement (including factors related to head straps or netting) or those present prior to stimulation. Second, there is no specified way of localizing side effects to ensure they are biologically relevant (e.g., under electrodes as opposed to areas affected by the straps/netting). Third, reliance on participant attribution (i.e., stating whether side effects were related to stimulation) is problematic, especially given the varying levels of insight clinical populations possess.

Supplemental materials provide a modified tolerability questionnaire and a description of our revised approach for evaluating side effects at different points during the stimulation session. While this questionnaire contains the same items as in Brunoni et al.’s [2] original version, we reordered side effects based on the frequency with which they were reported in the current study (starting with most common). We suspect this revised order will improve the accuracy of participants’ report. For example, a number of participants endorse “headache” when, in fact, they claimed that they meant a burning sensation or scalp pain when those items were subsequently queried. Additionally, participants are instructed to point to where they experienced a given sensation so that study team members can note whether the side effects were experienced under or around electrodes as opposed to distal head/body regions. This questionnaire is completed before impedances are measured (after electrodes are placed) and at the conclusions of stimulation (while electrodes are still in place). After the participant provides ratings, the examiner completes the “Post-tDCS Safety Questionnaire – Research Staff” which asks whether they believe endorsed side effects are related to tDCS and requires a brief justification for this decision.

This is among the first studies to document comparable tolerability and blinding for active and sham HD-tDCS. Findings support the use of 2 mA and 3 mA HD-tDCS with older adults, though more extensive and uniform data are needed to validate these conclusions.

Author declaration

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work. CUNY has patents on Brain Stimulation with MB as inventor, MB consults for Boston Disease Center (SP30AG053760). Partial results were presented at the 2017 and 2018 annual meetings of the International Neuropsychological Society.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2018.04.022.

References


[22] NACC PPA criteria.


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