



Adaptive current tDCS up to 4 mA

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ABSTRACT

Background: Higher tDCS current may putatively enhance efficacy, with tolerability the perceived limiting factor.

Objective: We designed and validated electrodes and an adaptive controller to provide tDCS up to 4 mA, while managing tolerability. The adaptive 4 mA controller included incremental ramp up, impedance-based current limits, and a Relax-mode where current is transiently decreased. Relax-mode was automatically activated by self-report VAS-pain score >5 and in some conditions by a Relax-button available to participants.

Methods: In a parallel-group participant-blind design with 50 healthy subjects, we used specialized electrodes to administer 3 daily session of tDCS for 11 min, with a lexical decision task as a distractor, in 5 study conditions: adaptive 4 mA, adaptive 4 mA with Relax-button, adaptive 4 mA with historical-Relax-button, 2 mA, and sham. A tablet-based stimulator with a participant interface regularly queried VAS pain score and also limited current based on impedance and tolerability. An Abort-button provided in all conditions stopped stimulation. In the adaptive 4 mA with Relax-button and adaptive 4 mA with historical-Relax-button conditions, participants could trigger a Relax-mode ad libitum, in the latter case with incrementally longer current reductions. Primary outcome was the average current delivered during each session, VAS pain score, and adverse event questionnaires. Current delivered was analyzed either excluding or including dropouts who activated Abort (scored as 0 current).

Results: There were two dropouts each in the adaptive 4 mA and sham conditions. Resistance based current attenuation was rarely activated, with few automatic VAS pain score triggered relax-modes. In conditions with Relax-button option, there were significant activations often irrespective of VAS pain score. Including dropouts, current across conditions were significantly different from each other with maximum current delivered during adaptive 4 mA with Relax-button. Excluding dropouts, maximum current was delivered with adaptive 4 mA. VAS pain score and adverse events for the sham was only significantly lower than the adaptive 4 mA with Relax-button and adaptive 4 mA with historical-Relax-button. There was no difference in VAS pain score or adverse events between 2 mA and adaptive 4 mA. **Conclusions:** Provided specific electrodes and controllers, adaptive 4 mA tDCS is tolerated and effectively blinded, with acceptability likely higher in a clinical population and absence of regular querying. Indeed, presenting participants with overt controls increases rumination on sensation.

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Introduction

With >1500 published reports in the past 5 years, transcranial Direct Current Stimulation (tDCS) is an exhaustively investigated interventional neurotechnology [1], but using limited intensities. Circa 2000, canonical studies used 1 mA intensity [2] and earlier clinical trials tested 2 mA [3]. Over the next two decades and across a breadth of indications, only current of 1–2 mA intensities have

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been tested [4,5] with limited exceptions. tDCS with 2.5 mA has been used in select clinical populations [5,6]. A case report of 3 mA over an extended period was considered safe [7]. In 16 healthy participants 3 mA tDCS, with topical anesthetic cream, was tolerated and produced intensity-specific neuromodulation [8]. A review of early evaluations of tDCS circa 1960 identified a single instance of 3 mA, with local anesthetic used [9]. High-definition tDCS (HD-tDCS) was tolerated at 3 mA [10] in a sample of older adults. 3 mA split across two HD-tDCS targets (1.5 mA each) was tolerated [11]. A single session of 4 mA tDCS was evaluated safe and tolerated in 3 stroke patients [12,13]. Brief 4 mA tDCS was applied to participants under general anesthesia with Deep Brain Stimulation (DBS) electrodes [14]. Twenty sessions of Adaptive 4 mA (using methods formulated here) was tolerated in 2 participants with major depression [15].

Evidence from animal studies suggest that 4 mA does not approach injurious limits [16,17]. The past decade has introduced advancements in tDCS electrode [18,19] and stimulator technology [20,21] that may increase tolerability at higher currents. Despite extensive evidence that 1–2 mA tDCS relevant electric field modulate neuronal function [22–25], benefits of moderately increasing current intensity have been debated [26].

We evaluated the total applied current and tolerability of three types of Adaptive 4 mA tDCS controllers; all types included adaptive ramps, impedance-based current mediation and a Relax-mode, but they differed in how Relax-mode was triggered: relying only on VAS pain score (condition 1: Adaptive 4 mA); relying on VAS pain score and participant activation of a Relax-button (condition 2: Adaptive 4 mA with Relax-button); relying on VAS pain score and participant activation of a Relax-button over the course of the session (condition 3: Adaptive 4 mA with historical-Relax-button). Total applied current and tolerability of the three adaptive conditions were also compared against 2 mA tDCS (condition 4) and sham tDCS (condition 5). tDCS was controlled by a customized tablet-based stimulator which, in all conditions, queried VAS pain and provided an Abort-button (activation will stop stimulation), and only in condition 2 and 3, a Relax-button was provided (activation will transiently decrease based on a control algorithm (Figs. 1,7)). The ideal adaptive controller maximizes current delivery (up to 4 mA) while maintaining tolerability and avoiding dropouts.

In a randomized single-blind parallel-group design, 50 healthy adults received three daily 11-min (30 s ramp up + 10 min sustained period + 30 s ramp down) tDCS session of their assigned condition, while engaging in a distractor task. We report all tested conditions were well tolerated. While a priori providing participant with Relax-button may expect enhanced tolerability, we report the opposite (despite reduced current), presumably reflecting increased rumination of sensation. The tolerability of Adaptive 4 mA condition (without Relax-button) was not significantly different from 2 mA of Sham tDCS. These results do not bear on 4 mA tDCS without our controller or use of different electrodes. Noting we accessed a healthy population; our outcomes may be conservative for acceptability in clinical populations. These results support further investigation of Adaptive 4 mA with appropriate device design, electrodes, supervision, and a system for exploring still higher currents. Portions of these results were previously presented in abstract form [27,28].

Materials and method

This study spans experimental measurement in participants, and an analysis of current, impedance, and self-reported tolerability and efficacy data.

Participants

The study was conducted in accordance to the protocols and procedures approved by the Institutional Review Board of the City College of New York, CUNY. Fifty healthy participants (37 males and 13 females; age 19–34 years; mean age 24.7 ± 4.9) were enrolled in this participant-blind study. Participants with any evidence of skin disorders or sensitive skin (e.g. eczema, severe rashes), blisters, open wounds, burns including sun-burns, cuts or irritation (e.g. due to shaving), or other skin defects which compromise the integrity of the skin at or near stimulation locations were excluded from this study. All participants provided written informed consent to participate in the study. Participants were seated in an upright relaxed position throughout the stimulation.

Sensation and adverse events

Self-reporting questionnaires completed by the participants before and after each session (Table 1) assessed the extent of adverse events including headaches, nausea, neck pain, scalp pain, tingling, burning sensation, itching sensation, sleepiness, trouble concentrating, and dizziness on an intensity rating scale from 1 to 4 (1 = absent, 2 = mild, 3 = moderate, and 4 = severe). In addition, participants quantified their experienced adverse events in relationship to tDCS on a scale from 1 to 5 (1 = none, 2 = remote, 3 = possible, 4 = probable, and 5 = definite). VAS (Visual analogue scale) pain score (scale: 0–10; 0: no pain, 10: intolerable pain) was collected every 2 min during the stimulation via a built-in VAS graphical user interface (GUI) of the tablet-based stimulator.

Participant feedback for stimulation

The participants can provide feedback through the stimulation tablet GUI with two buttons: (1) The Relax-button which transiently decreases the current to minimize the participant's discomfort-available in condition 2 (Adaptive 4 mA with Relax-button) and condition 3 (Adaptive 4 mA with historical-Relax-button); (2) The Abort-button which linearly ramps down the tDCS current to 0 mA at the rate of 0.1 mA per 3 s till the session terminates, was available in all conditions. All participants were instructed that they could activate the Abort-button at any time during the stimulation if, they experienced any discomfort, or their VAS pain score was >7 , or they wished to stop stimulation for “any reason or no reason at all”. In addition, participants in condition 2 (Adaptive 4 mA with Relax-button) and condition 3 (Adaptive 4 mA with historical-Relax-button) were instructed that the Relax-button could be activated in an event of VAS pain score >5 . Effectively, participants were permitted to activate the Relax-button as often as they wanted regardless of pain perception, which could result in an excessive Relax activation (see Results). Participants were also prompted every 2 min to score VAS pain. Finally, the Abort or the Relax-mode were automatically triggered, if the reported VAS pain score was 7 or higher (Abort), and 5 or higher (Relax-mode) respectively.

Adaptive 4 mA controller

All conditions where the current target was 4 mA used an adaptive controller and logic (i.e. in none of the cases current simply ramped up linearly to 4 mA). The Adaptive 4 mA controller includes parallel functions (Fig. 1) of: 1) step-wise ramp up; 2) Impedance-based current moderation; 3) Relax-mode current moderation; 4) Abort trigger. The overall rationale for this controller (testing it was the primary objective of this study) was to maximize current delivery while maintaining tolerability.

Table 1
Summary of participant reported adverse events as intensity and perceived relationship to tDCS.

Condition	Adverse Events	Headache	Neck pain	Scalp pain	Tingling	Burning Sensation	Itching	Sleepiness	Trouble concentrating	Dizziness	Nausea
Adaptive 4 mA	Intensity (mean ± SD)	(1.13 ± 0.35)	(1.06 ± 0.26)	(1.20 ± 0.56)	(1.46 ± 0.64)	(1.53 ± 0.74)	(1.46 ± 0.64)	(1.20 ± 0.41)	(1.00 ± 0.00)	(1.00 ± 0.00)	(1.15 ± 0.36)
	Relation (mean ± SD)	(1.00 ± 0.00)	(1.00 ± 0.00)	(1.26 ± 1.03)	(1.80 ± 1.65)	(1.73 ± 1.53)	(1.46 ± 1.25)	(1.00 ± 0.00)	(1.00 ± 0.00)	(1.00 ± 0.00)	(1.10 ± 0.30)
Adaptive 4 mA with Relax-button	Intensity (mean ± SD)	(1.06 ± 0.26)	(1.06 ± 0.25)	(1.33 ± 0.48)	(1.00 ± 0.86)	(1.40 ± 0.63)	(1.93 ± 0.96)	(1.13 ± 0.35)	(1.06 ± 0.25)	(1.20 ± 0.56)	(1.00 ± 0.30)
	Relation (mean ± SD)	(1.26 ± 0.70)	(1.26 ± 0.70)	(1.73 ± 1.38)	(2.46 ± 1.76)	(2.00 ± 1.55)	(2.86 ± 1.95)	(1.00 ± 0.00)	(1.00 ± 0.00)	(1.13 ± 0.52)	(1.00 ± 0.00)
Adaptive 4 mA with historic-Relax-button	Intensity (mean ± SD)	(1.06 ± 0.26)	(1.13 ± 0.52)	(1.33 ± 0.62)	(1.67 ± 0.49)	(1.20 ± 0.41)	(2.13 ± 1.25)	(1.27 ± 0.46)	(1.20 ± 0.41)	(1.13 ± 0.35)	(1.00 ± 0.00)
	Relation (mean ± SD)	(1.06 ± 0.26)	(1.00 ± 0.00)	(1.60 ± 1.12)	(3.00 ± 1.69)	(1.33 ± 0.90)	(2.93 ± 1.83)	(1.13 ± 0.35)	(1.13 ± 0.52)	(1.40 ± 1.12)	(1.00 ± 0.00)
2 mA tDCS	Intensity (mean ± SD)	(1.20 ± 0.41)	(1.06 ± 0.26)	(1.06 ± 0.26)	(1.53 ± 0.74)	(1.46 ± 0.74)	(2.00 ± 0.75)	(1.33 ± 0.49)	(1.40 ± 0.63)	(1.06 ± 0.26)	(1.15 ± 0.36)
	Relation (mean ± SD)	(1.00 ± 0.00)	(1.00 ± 0.00)	(1.00 ± 0.00)	(1.13 ± 0.52)	(1.40 ± 0.82)	(1.86 ± 1.30)	(1.00 ± 0.00)	(1.13 ± 0.52)	(1.00 ± 0.00)	(1.10 ± 0.30)
Sham	Intensity (mean ± SD)	(1.13 ± 0.35)	(1.17 ± 0.36)	(1.13 ± 0.35)	(1.33 ± 0.62)	(1.13 ± 0.35)	(1.73 ± 0.70)	(1.10 ± 0.28)	(0.00 ± 0.00)	(1.06 ± 0.26)	(1.00 ± 0.00)
	Relation (mean ± SD)	(1.13 ± 0.99)	(1.00 ± 0.00)	(1.46 ± 1.24)	(1.60 ± 1.29)	(1.53 ± 1.41)	(2.13 ± 1.59)	(1.00 ± 0.00)	(0.00 ± 0.00)	(1.06 ± 0.25)	(1.00 ± 0.00)

When stimulation is initiated, the incremental ramp up initiates with a linear ramp up to 2 mA over 30 s. Impedance-based current moderation not by the Relax-mode is active during this first 30 s. Current is increased from 2 to 4 mA in a step-wise fashion where current is sustained for 15 s and then ramped up in 0.5 mA increments over 15 s. With each increment taking 30 s, and 4 increments from 2 to 4 mA, the minimum time for current to attain 4 mA from 2 mA increment is 120 s. The minimum time to start stimulation at 4 mA is therefore 150 s.

The impedance-based current mediation is active during all times of stimulation. If impedance is > 20 kΩ threshold during the ramp up to 2 mA, or > 20 kΩ threshold during the ramp from 2 mA to 4 mA, or > 10 kΩ threshold at the 4 mA target, then current is reduced proportionally to the resistance increase above the threshold. If impedance decreases below this threshold, impedance-based mediation stops.

The Relax-mode is triggered either automatically by a VAS pain score of > 5 or participant activation of the Relax-button, when available. In the simplest implementation, when triggered, the Relax-mode ramps down the current by a 0.5 mA to the last sustained increment current for 15 s (Condition 1, Adaptive 4 mA; Condition 2, Adaptive 4 mA with Relax-button) or 10 s (Condition 3, Adaptive 4 mA with historical- Relax-button), sustains the reduced current for a minimum of 15 s, and then ramps up the current back to the initial value over 15 s. Relax-mode can be triggered during the ramp up where it effectivity throttles, but does not stop the general increase. This mode can also be activated repeatedly except during the 15 s or 10 s ramp down and when otherwise disabled (during the first 30 s ramp up). Triggering a second Relax-mode while the current is ramping down from the first Relax-mode has no effect on the prior ramp down. In the adaptive 4 mA (where Relax-mode is only activated automatically) and adaptive 4 mA with Relax-button, the duration of reduced current is sustained for fixed 15 s, while in the adaptive 4 mA with historical- Relax-button, the duration of reduced current is sustained according to equation (1).

Duration of current sustained at dampened level (s)

$$= 30 * [\text{no. of times Relax – button activated}] - 15 \quad (1)$$

As aforementioned, VAS pain score > 7 or participant activation of Abort-button, when available, automatically triggered the Abort. Once triggered, current ramps down to zero current level and the sessions ends. *Stimulation Conditions.*

Participants were randomly assigned to one of the five treatment conditions: Condition 1, Adaptive 4 mA stimulation; Condition 2, Adaptive 4 mA with Relax-button; Condition 3, Adaptive 4 mA with historical-Relax-button; Condition 4, 2 mA tDCS; Condition 5, Sham. A M1-SO montage was used with anode placed over the left primary motor cortex (C3: EEG 10–20) and cathode placed over the contralateral-supraorbital (Fp2: EEG 10–20) for all treatment conditions. Current was administered for 11 min (including 30 s of ramp up and down each and a 10 min sustained period) using a specialized device (Soterix Medical Inc., New York, USA; Ybrain Inc, Seongnam-si, Republic of Korea) of a tablet-based tDCS stimulator with GUI participant interface, snap-headgear (which ensured placement [29]), and single-use pre-saturated 5 × 5 cm snap electrodes EasyPad, Soterix Medical Inc., New York, USA).

The 11 min sessions were considered more than long enough to encompass period of impedance transients [1,20,30] and maximal self-report sensation [31]. This study was not intended to resolve acute or lasting changes in brain function. A parallel-group design was used to avoid confounds from participants recognizing difference across conditions (e.g. being provided a Relax-button only in some conditions) and increase reliability or testing for changes

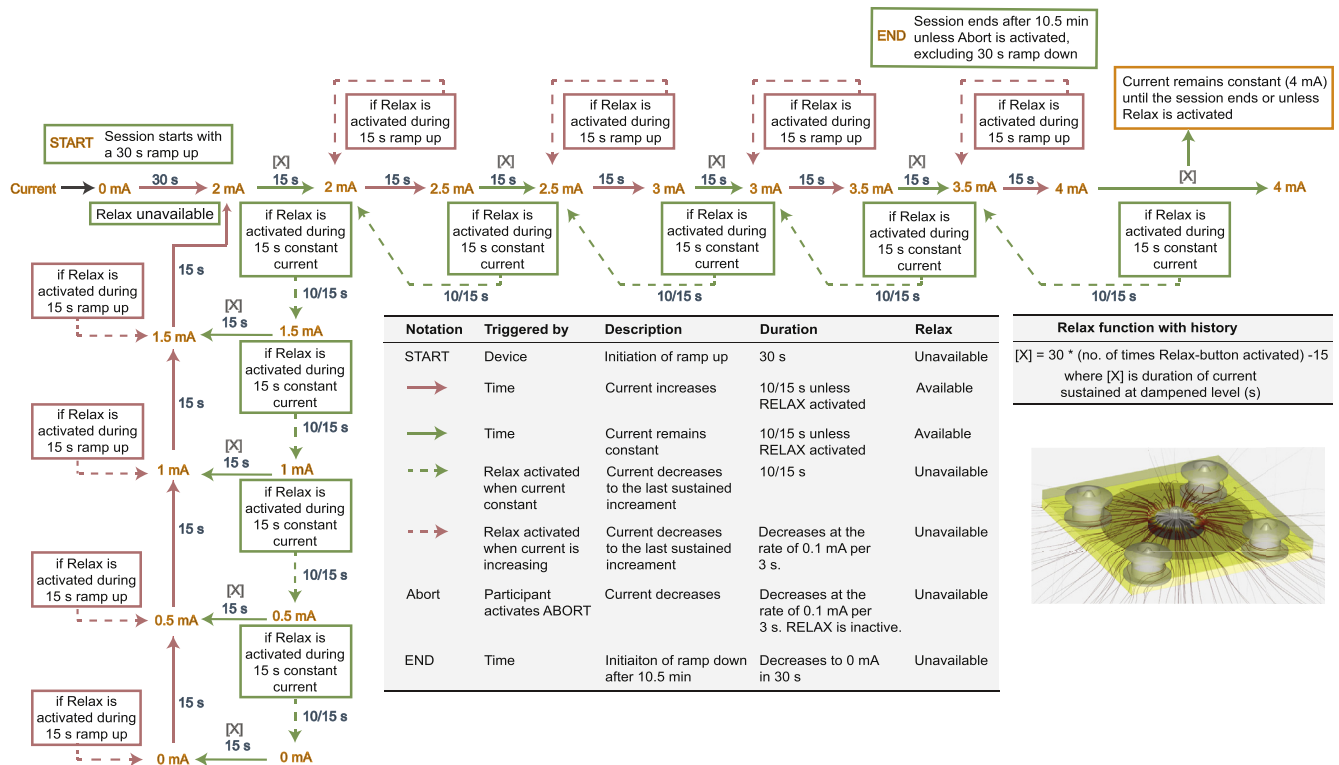


Fig. 1. 4 mA Adaptive Algorithm and Logic for Current Control. The current intensity transiently increases over time up to 4 mA with 15 s intervals of constant current phase followed by an increment of current intensity by 0.5 mA over a duration of 15 s. The Relax-button lowers the current for 10/15 s (depending upon the stimulation conditions) to the last sustained current intensity and then the current creeps back up after 15 s. The Abort-button terminates stimulation session and ramps down the current to 0 mA over a period of 30 s. The goal of the cyclical logic diagram is to obtain a well-tolerated optimal current intensity. (*Inset*) Optimized electrode with 5 rivets. FEM simulation of current streamlines showing current density is distributed.

across repeated sessions. Three repeated sessions, with at least one day interval, were considered sufficient to resolve any immediate (e.g. after one session) change in tolerability based on repetition (session number) across conditions. Scalp current and impedance were automatically queried in real-time upon the onset of stimulation by the smart stimulator and stored in cloud for later analysis (Fig. 7).

Condition 1 Adaptive 4 mA: In this mode of stimulation, the current ramps up to 4 mA using an incremental ramp (Fig. 2A). The ramp up and sustained phase are limited based on impedance and VAS pain score (as needed) (Fig. 2B, 2C). The incremental ramp starts with a ramp up to 2 mA over 30 s during which Relax-mode is disabled, and then ramps up to 4 mA over a minimum (if Relax-mode is not triggered) of 120 s. The 2–4 mA ramp up is step-wise according to the adaptive controller logic (if Relax-mode is not activated): the current at 2 mA is sustained for 15 s and then linearly increases the current to 2.5 mA over 15 s, with this rule is repeated till the intended 4 mA current intensity is attained (Fig. 1). The adaptive 4 mA ramp up is thus a total of 150 s. In the participant GUI, the Abort-button is always available, but in this condition the Relax-button is not. Therefore, in the Adaptive 4 mA condition, the Relax-mode current mediation can only be triggered automatically by a VAS pain score of >5 (Fig. 2C). As in all conditions, Abort is automatically triggered by a VAS pain score >7.

Condition 2 Adaptive 4 mA with Relax-button: This mode is similar to Adaptive 4 mA with the addition of a Relax-button that participants can activate ad libitum, though in principle they are instructed to do so only under significant discomfort (VAS pain score > 5) (Fig. 3). After the 30 s ramp up to 2 mA, activating Relax-button triggers the transient Relax-mode current mediation. Relax-mode is also automatically activation by a VAS pain score >5 (Fig. 3C). The Abort-button is available.

Condition 3 Adaptive 4 mA with historical-Relax-button: This mode is similar to Adaptive 4 mA with Relax-button, however, after completion of a Relax-mode triggered ramp down (10 s), the current is sustained at this dampened level for a time that increases with the number of prior Relax-mode activation (equation (1)) (Fig. 4). For example, activation of Relax-mode twice (by activating Relax-button or VAS pain score > 5) will sustain the reduced current for 45 s. The Abort-button is available.

Condition 4 2 mA tDCS: This mode is a conventional 2 mA tDCS mode of stimulation but with impedance-based current mediation (Fig. 5). Current ramps up linearly to 2 mA over 30 s, and is sustained for 10 min, before ramping down linearly over 30 s. The Abort-button is available.

Condition 5 Sham stimulation: In this conventional mode of sham stimulation, current ramps up linearly to 2 mA over 30 s and then immediately ramps down over 30 s (Fig. 6). The Abort-button is available.

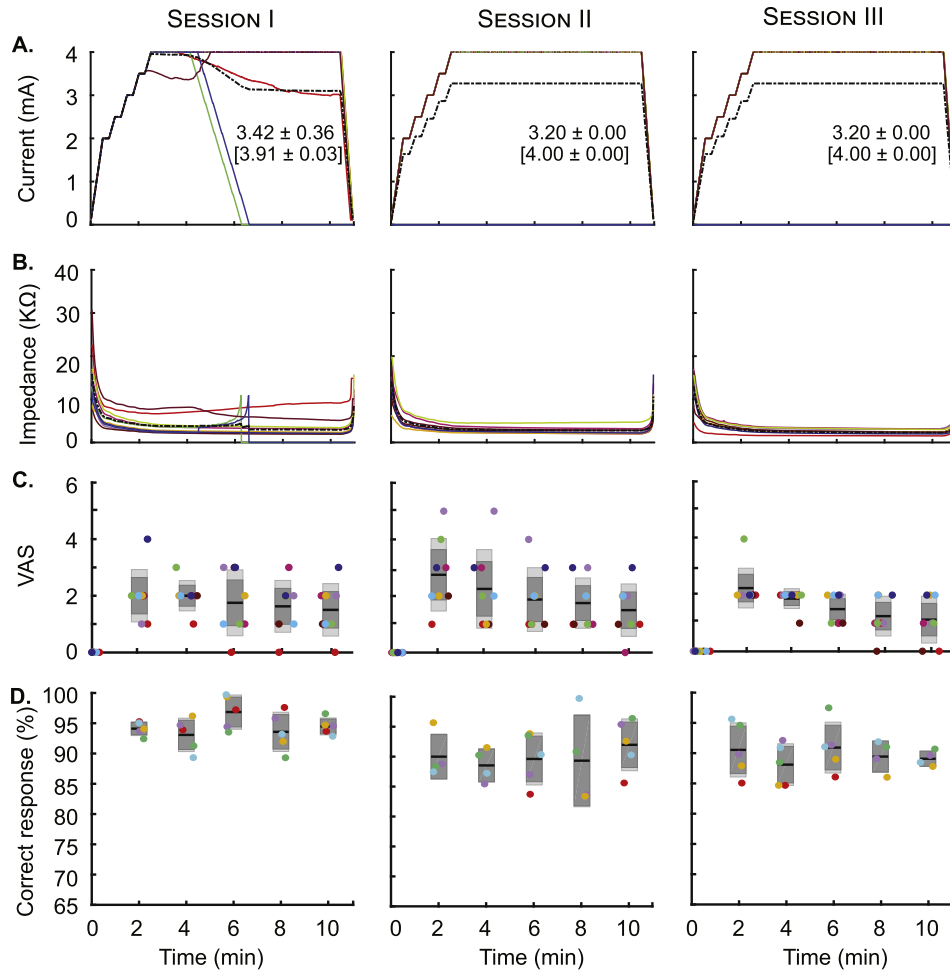


Fig. 2. Current waveform, impedance, VAS pain score, and lexical decision task for Adaptive 4 mA condition. Participants per condition are color coded. Current ramps up and maintains to a 4 mA target with adaptive logic, (automatic only) VAS pain score-based Relax-mode activation, and impedance-based current moderation. (A) Current applied. There were 2 dropouts during session I (green and blue traces). Also, in session I there were 2 impedance-based current reduction (red and brown traces). Average traces (dashed line) and current values without the parenthesis represents condition including dropouts. Values within parenthesis represent average session current excluding dropouts. (B) Impedance. Average impedance across sessions was <10 kΩ. (C) Participant VAS pain score collected before and every 2 min during stimulation. Average VAS pain score across sessions was ≤ 3 with no instance of VAS pain score >5 . (D) Correct response range for the lexical decision task, scored every 2 min during stimulation, was 89–100%. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Lexical decision task

During the stimulation session, the participants engaged in a lexical decision task [32] as a distractor (Figs. 2D, 3D, 4D, 5D, 6D). On the computer screen separate from the tDCS device GUI, participants were presented with a mixture of words (e.g. *canorous*) and pseudowords (nonsense strings that represent the phonotactic rules of a language, like “*trud*” in English) and asked whether the presented stimulus was a word or not. The lexical decision task was paused every 2 min when participants were prompted to report the VAS pain score.

Statistical analysis

Normality test of VAS score and adverse events responses were tested using Shapiro-Wilk tests with Lilliefors significance correction. A corresponding parametric (ANOVA) or non-parametric (Kruskal-Wallis test) determined the significance of the data. When significant, post-hoc pairwise comparison was conducted using parametric Tukey’s HSD test or non-parametric Dunn’s test to find the difference between groups. A critical value (P) of <0.05 was accepted as a significant difference between the groups. MATLAB

function “*rmoutliers*” detected and removed outliers from the data based on mean (outlier defined as an element of a given dataset more than 3 standard deviations from the mean). Note that no outliers were detected for any primary outcome measures or for statistical test, but outliers were identified on lexical decision task (reflecting participants not engaging in the task) and were removed for graphing purposes.

Results

A total of 144 treatment sessions were completed. No serious adverse events were reported in the entire study. There were two aborts in the first session of the adaptive 4 mA waveform (no Relax-button) condition. In Sham stimulation (condition 5), there was one abort in session II and one abort in session III. Per study design, participants who activate Abort-button withdrew from the rest of the sessions, regardless of their willingness to continue. Across all conditions and sessions, there were no instances of VAS pain score ≥ 7 (including in the participants who activated Abort-button), which would trigger an automatic Abort. Adverse events, VAS pain scores, lexical decision task performance, current, and

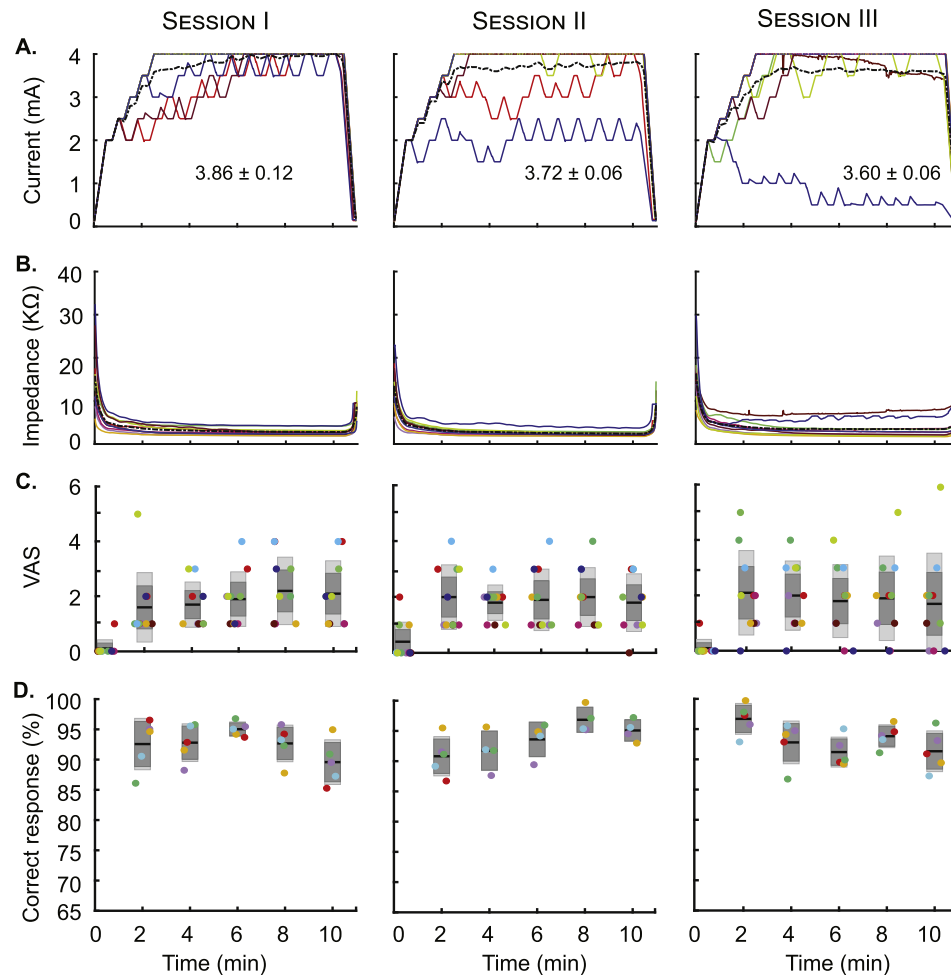


Fig. 3. Current waveform, impedance, VAS, and percentage of correct response for the Adaptive 4 mA with Relax-button condition. Participants per condition are color coded. Current ramps up and maintains to a 4 mA target with adaptive logic, automatic (VAS pain score-based) and participant activated Relax-mode, and impedance-based current moderation. (A) Current applied. Reductions in current are associated with participant Relax-button activation used by a minority of participants (but repeatedly). A single instance of VAS pain score >5 was reported at the end of session III. (B) Average impedance was <10 kΩ for all participants across sessions. (C) Average VAS score collected before and every 2 min during stimulation, across sessions was ≤ 2 . Once instance of VAS pain score >5 at the end of session III (green dot). (D) Range of correct response of lexical decision task, scored every 2 min during stimulation was 86–100%. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

impedance across every sessions of the study conditions were reported.

Current and impedance

We analyzed the current intensities, both including and excluding the dropouts for the Adaptive 4 mA (no Relax-button) condition. Current intensities including the dropouts for the Adaptive 4 mA condition for sessions I, II, and III were 3.42 ± 0.36 , 3.20 ± 0.00 , and 3.20 ± 0.00 , respectively (Fig. 2). Excluding the dropout, the current intensities for this session I, II, and III were 3.91 ± 0.03 , 4.00 ± 0.00 , and 4.00 ± 0.00 , respectively. There were no instances of VAS pain score >5 (which triggered an automatic Relax-mode) across sessions. There were 2 instances across sessions where impedance-based current mediation was active for at least 1 s (see Fig. 3).

The current intensities (mean \pm SD) for adaptive 4 mA with Relax-button were 3.86 ± 0.12 , 3.72 ± 0.06 , and 3.60 ± 0.06 for session I, II, and III, respectively. This reduction in current from the 4 mA target reflected Relax-button activation by a minority participant. These participants activated Relax-button repeatedly, while not reporting high VAS pain score. Across sessions, there was 1 instance of VAS pain score >5. There was 1 instance across

sessions where impedance-based current mediation was active for at least 1 s. No participant activated the Abort-button.

For Adaptive 4 mA with historical-Relax-button, the current intensities for session I, II, and III were 2.99 ± 0.07 , 2.91 ± 0.07 , and 3.10 ± 0.07 , respectively. This reduction in target current (4 mA) reflected Relax-button activation. There was no Abort-button activation and no instance of impedance-based current mediation across sessions. Across sessions, there were 9 total instances of VAS pain score >5 (which triggered automatic Relax-mode).

For 2 mA stimulation, the current intensities for session I, II, and III were 2.00 ± 0.00 , 1.98 ± 0.00 , and 2.00 ± 0.00 , respectively. The reduction in current for session II reflects 1 instance of impedance-based reduction. For 2 mA stimulation condition, there were no instance of VAS pain score >5.

In Sham stimulation, there were no instance of VAS pain score >5 (though as noted, 2 dropouts following Abort-button activation) and 2 instances across sessions in which impedance-based current mediation was active (always during the ramp up/down).

Average impedance in all study conditions except the sham condition was <10 kΩ across sessions. For Sham stimulation, the average impedance excluding ramp down was >20 kΩ across sessions, reflecting the nature of impedance measurement (not unusual conditions).

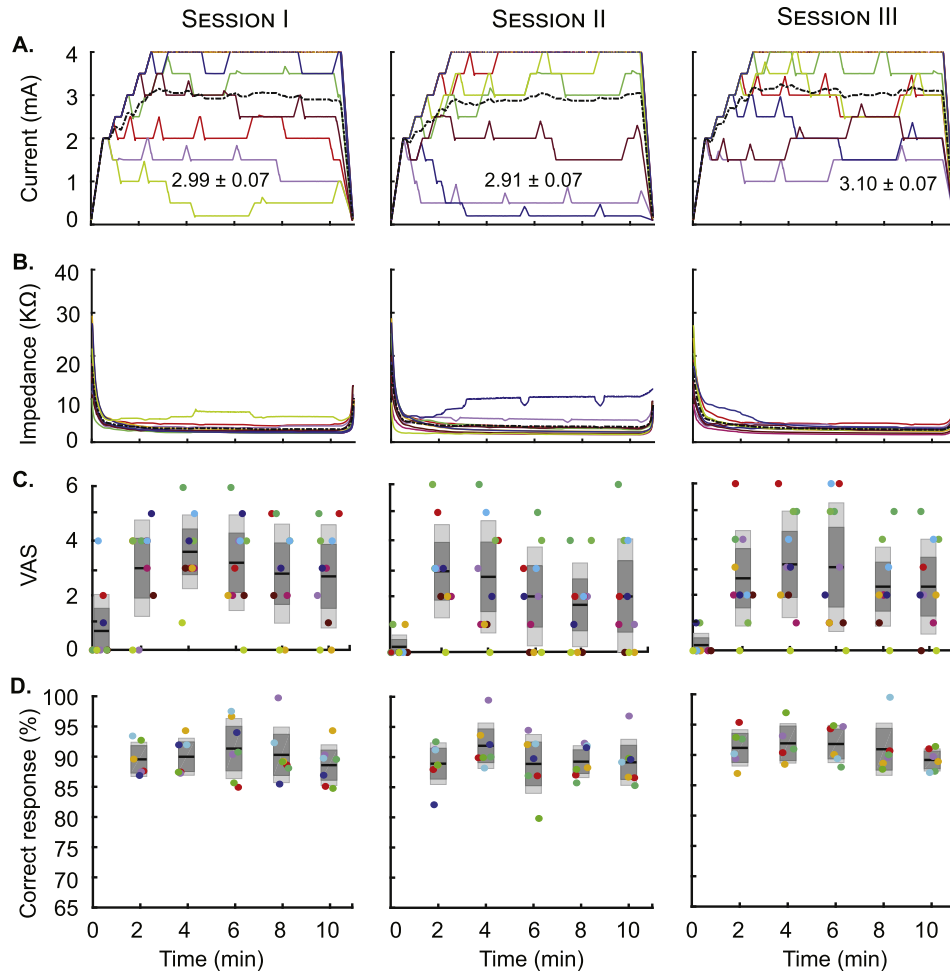


Fig. 4. Current waveform, impedance, VAS, and lexical decision task for Adaptive 4 mA with historical-Relax-button condition. Participants per condition are color coded. Current ramps up and maintains up to a 4 mA target with adaptive logic, automatic (VAS pain score-based) and participant activated Relax-mode, and impedance-based current moderation. With increasing number of Relax-button activation, the duration of current moderation increases. (A) Current applied. Reductions in current are associated with participant activation of Relax-button and there were 9 instances of VAS pain score >5 triggering an automatic Relax-mode. (B) Average impedance was <10 kΩ. (C) Average VAS pain score, collected before and every 2 min during stimulation, across sessions was ~3. The highest VAS pain score was 6 reported by 4 participants (green, light blue, red, dark blue), a total of 9 instances. (D) Percentage of current response of the lexical decision task, scored every 2 min during stimulation, ranged from 80 to 100%. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

A two-way ANOVA tested the significant difference in the current intensities across different treatment groups. Including the dropouts (of the Adaptive 4 mA and Sham conditions), there was a statistically significant difference in group means among the study conditions, $F(4, 8) = 868.84$, $P < 0.05$. The mean current intensities across each study conditions were significantly different from all others (Tukey's HSD test; $P < 0.05$). In this analysis including the dropouts, Adaptive 4 mA with Relax-button condition has more current for each session (I: 3.86 ± 0.12 ; II: 3.72 ± 0.06 ; III: 3.60 ± 0.06) compared to other conditions. Interactions between the session number and study condition on current intensity was not significant, $F(2, 8) = 1.5633$, $P > 0.05$. Excluding the drop-outs, the main effect of study conditions on mean current intensity was significant ($F(4, 8) = 1126$, $P < 0.05$). Mean current intensities across conditions were different from all others ($P < 0.05$). In this analysis excluding the dropouts, Adaptive 4 mA condition provided significantly more current in all three sessions (I: 4.00 ± 0.00 ; II: 4.00 ± 0.00 ; III: 4.00 ± 0.00 ; $P < 0.05$) than Adaptive 4 mA with Relax-button condition. There was no significant interaction between the session number and the study condition ($F(2, 8) = 0.16$, $P > 0.05$).

Adverse events

Frequently reported adverse events were skin itching, tingling, and mild burning sensations (see [supplemental figures X and Y](#)). A non-parametric Kruskal-Wallis tested the significant difference in adverse events among the study conditions. There was no significant difference in the adverse events intensity among the five study conditions ($\chi^2 = 2.3$, $df = 4$, $P > 0.05$). However, across study conditions, adverse events intensity in relationship to tDCS was significantly different ($\chi^2 = 11.6$, $df = 4$, $P < 0.05$). Conventional 2 mA (mean rank = 21.0) and Adaptive 4 mA (mean rank = 25.65) conditions both had lower adverse events in relationship to tDCS ($P < 0.05$) than the Adaptive 4 mA with Relax-button (mean rank = 33.85) condition. Sham condition had lower adverse events in relationship to tDCS ($P < 0.05$) than adaptive 4 mA with historical-Relax-button and adaptive 4 mA with Relax-button conditions.

VAS pain score

The VAS pain score was statistically significant amongst the stimulation conditions ($\chi^2 = 49.71$, $df = 4$, $P < 0.05$, Kruskal-Wallis

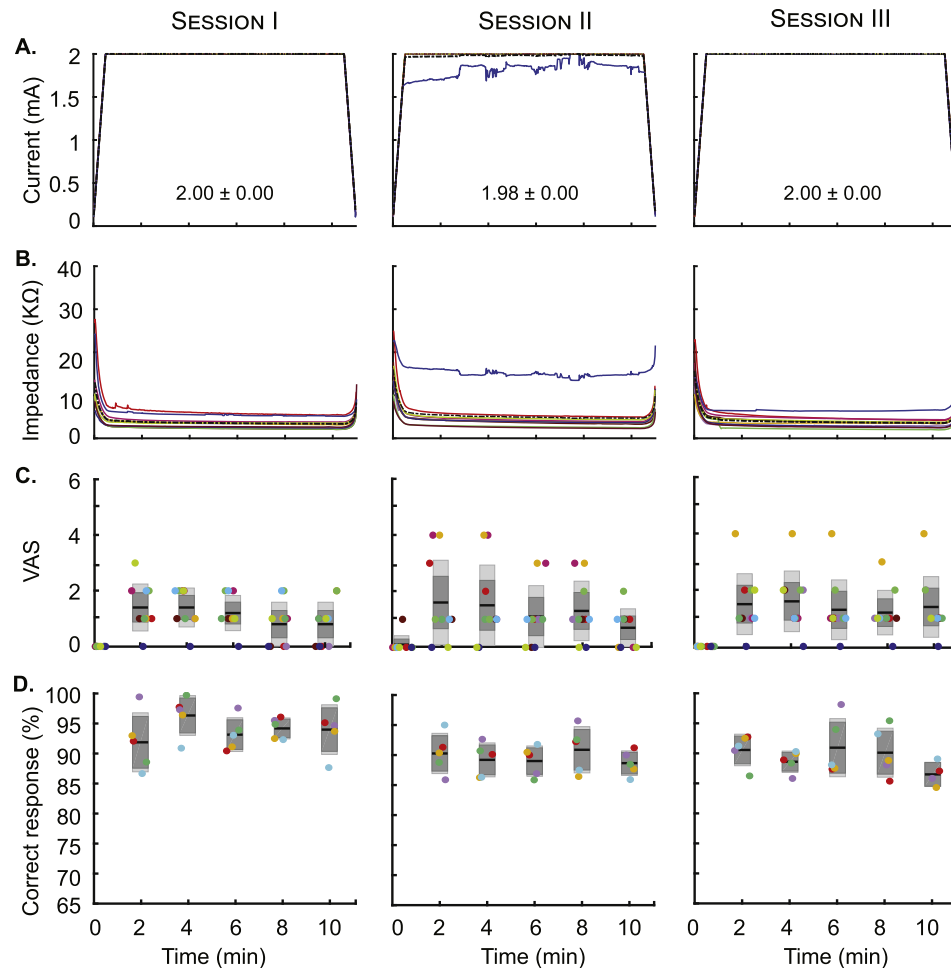


Fig. 5. Current waveform, impedance, VAS, and lexical decision task for 2 mA stimulation condition. Participants per condition are color coded. Current ramps up and maintains to a 2 mA target with impedance-based current moderation (A) Current waveform. (B) Impedance. There was one session with impedance-based current reduction in session II (blue trace). (C) Average VAS pain score was <2 across all sessions with no instance of VAS pain score > 4. (D) Range of correct response of the lexical decision was 85–100%. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

test; VAS mean rank: Sham (34.23); Adaptive 4 mA with historical-Relax-button (106.88); Adaptive 4 mA with Relax-button (92.52); 2 mA (64.68); Adaptive 4 mA waveform (79.18)). VAS pain score for the Sham condition was significantly lower ($P < 0.05$) than the Adaptive 4 mA, Adaptive 4 mA with Relax-button and the Adaptive 4 mA with historical-Relax-button. Conventional 2 mA tDCS had lower VAS pain score than Adaptive 4 mA with historical-Relax-button. There was no significant difference among the other remaining stimulation conditions ($P > 0.05$). Interactions between the session number and stimulation condition on VAS pain score was not significant ($\chi^2 = 0.4$, $df = 2$, $P > 0.05$) and didn't vary significantly across sessions for all stimulation conditions ($P > 0.05$).

Lexical decision task

The subjective response of the lexical decision task for each study condition was reported as correct response percentage across sessions (min and max) as: Adaptive 4 mA (max: 100%; min: 89%), Adaptive 4 mA with Relax-button (max: 100%; min: 86%), Adaptive 4 mA with historical-Relax-button (max: 100%; min: 80%), 2 mA tDCS (max: 100%; min: 85%), Sham (max: 100%; min: 84%). The average correct response percentage was >90% across all stimulation conditions. Our study was not designed to resolve condition-specific effects on task; indeed, in some cases participants

temporarily stopped engaging in the task (e.g. distraction, boredom) resulting in artifactual score reduction.

Discussion

Our results provide evidence in support for the tolerability of Adaptive 4 mA tDCS and so the feasibility of trials to test efficacy of higher dose tDCS. We do not identify a significant difference in subjective tolerability (VAS, adverse events) between Adaptive 4 mA, 2 mA, and Sham conditions. Tolerability across these conditions is also broadly consistent with prior reports using 2 mA [10,18,33–35]. Our results should only be interpreted inclusive of our specific tDCS techniques including current escalation algorithm in 4 mA conditions (Fig. 1), impedance-based current moderation and high-performance single-use electrodes across conditions, and other study design specifics discussed next.

Participants were informed that the purpose of this study was to evaluate their discomfort during the session and investigate the tolerability aspects of tDCS, and were queried regularly on VAS pain score. This design, despite the distractor task, may have encouraged rumination on sensation thereby compromising self-reported tolerability. Indeed, in the two conditions where a Relax-button was offered to the participants (Adaptive 4 mA with Relax-button and Adaptive 4 mA with historical-Relax-button), tolerability was

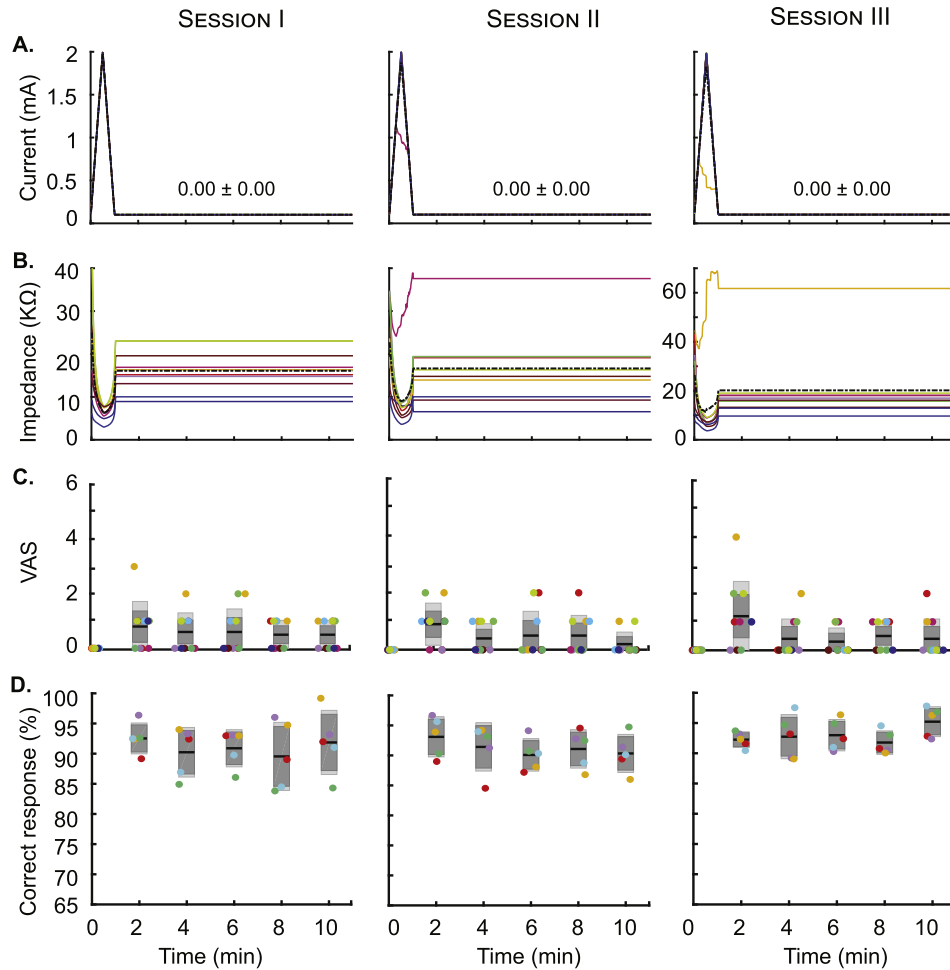


Fig. 6. Current waveform, impedance, VAS pain score, and lexical decision task for Sham stimulation condition. Participants per condition are color coded. Current ramps up and down from a 2 mA target. (A) Current waveform. There was one abort each in session II and session III. (B) Impedance. Relatively higher impedances reflect dependence on test current level. There was one impedance-based current reduction during the ramp up-down in session II. (C) Average VAS pain score, collected before and every 2 min during stimulation, was ≤ 1 across all sessions. (D) Range of correct response of the lexical decision, scored every 2 min during stimulation, was 84–100%. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

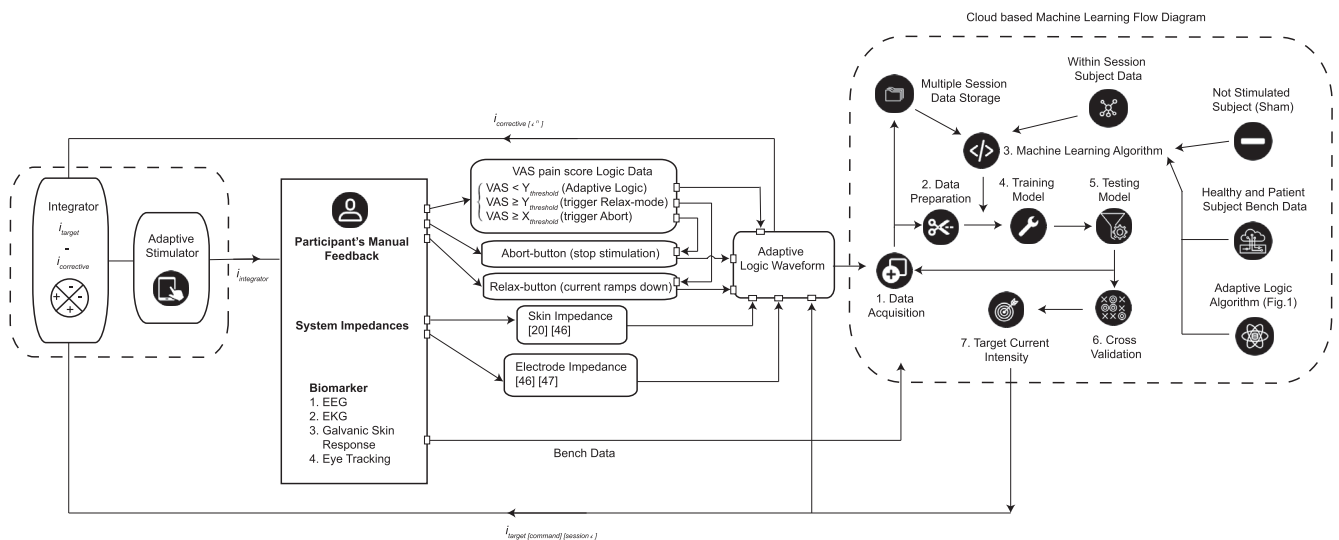


Fig. 7. Concept for cloud based machine-learning Adaptive tDCS optimization. Optimized dosage and tolerability profile are maintained for efficacy of tDCS using an Adaptive Logic Waveform tailored from participant's manual feedbacks (VAS pain score, Abort-button, or Relax-button activation), automatic VAS pain score-based Relax-mode and Abort, system impedance (skin impedance [20,46] and electrode impedance [46,47]), and biomarkers (EEG, EKG, galvanic skin response, eye tracking etc.). This waveform data is further processed via a cloud-based machine learning step to train, test, and validate the target current intensity for individualized tDCS. A smart cloud based current regulator device integrates the current output and other data collected from the participants.

poorer compared to both Adaptive 4 mA and even conventional 2 mA. A clinical population may be more motivated and accepting [36,37] of mild adverse effects than our cohort of healthy young adults. Indeed, in a pilot clinical trial of Adaptive 4 mA, 20 sessions were all completed and tolerated (average VAS pain score of 1.1–1.6, max 3) in two participants with major depression [15] – Relax-button (and Abort-button) were only in a physician directed controller, with no instance of request to activate by participants.

We are not aware of prior tDCS studies with Abort or Relax buttons being overtly presented to participants in an integrated GUI device. All four study-dropouts followed activating Abort-button – two each in the Sham and Adaptive 4 mA conditions – never associated with especially high VAS pain score. Relax-mode activation was also not well correlated with VAS pain score and not reflecting instructions to activate Relax-button at VAS pain score >5. Activation of Relax-button by some participants approached the maximum allowed iterations under Adaptive 4 mA with Relax-button (~10 times) and Adaptive 4 mA with historical-Relax-button (~4 times) suggesting continual Relax-button activation, even at current below 1 mA. Thus, when and how to include these features in Adaptive 4 mA trials is complicated.

We report no significant difference in VAS pain score or adverse events between Sham condition, 2 mA, and Adaptive 4 mA conditions. Given general discussions on the reliability of sham protocols in tDCS [33,38–42], this warrants brief commentary. Foremost, the reliability of sham depends on tolerability of the active tDCS arm which is determined by electrode design and application protocols. Here, we used electrodes optimized for tDCS, that are single-use and pre-prepared (saturated, no assembly) for consistency (Fig. 1). Second, the success of a sham arm in any given experiment is predicated on the overall study design (including how blinding success is defined) and not only perfectly replicating side-events. Indeed, since current evidently produces sensation, under sufficiently persnickety experimental design (including if we significantly increased participant number), participants will resolve differences between any doses.

The system developed and verified here, using Adaptive ramp, impedance-based current moderation, Relax-mode, and optimized electrodes may support testing of still higher current intensities, including in clinical populations. Providing participants control over the tDCS dose has implications for trial design – but dose titration, whether by clinician or patients, is universal across neuromodulation approaches [43,44] with the exception of tDCS. Interestingly, our trial shows providing participants with such control does not necessarily enhance tolerability. The present study on tolerability is ambivalent to the benefits of higher currents [45] but provides a system supporting dose-response studies that underpin intervention optimization, which have been curtailed to a limited range in tDCS.

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Conflicts of interest

The City University of New York (CUNY) has IP on neuro-stimulation system and methods with author, NK and MB as inventors. MB advises Boston Scientific, GlaxoSmithKline, and Mecta. MB has equity in Soterix Medical Inc. KL is a co-founder of Ybrain Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2019.07.027>.

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