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Methods for extra-low voltage transcranial direct current stimulation: Current and time dependent impedance decreases

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HIGHLIGHTS

- Transcranial direct current stimulation is accompanied by a characteristic drop in skin impedance which significantly reduces compliance voltage.
- Skin impedance changes have been investigated experimentally and approximated by a 4th order linear model.
- Reduced-voltage and Limited Total Energy tDCS are viable approaches towards more protective and robust brain stimulation protocols.

ABSTRACT

Objective: Though tDCS is well tolerated, it is desirable to further limit the voltage applied for additional safety factors and optimized device design. We investigated the minimum voltage required for tDCS using 1.5 and 2.5 mA.
Methods: Impedance data has been collected prior to, during and after 18 tDCS sessions, using 1.5 mA and 2.5 mA tDCS currents and three different test current magnitudes. Data was pooled and tested for differences using *t*-tests, corrected for multiple comparisons. Average impedance data was fitted into a RLC circuit model with additional double integrator.
Results: We report that the impedance drop during tDCS initiation significantly reduces the voltage compliance required to achieve the target current (14.5 V for 1.5 mA, 18.5 V for 2.5 mA). Data was well approximated by a 4th order linear impedance model.
Conclusion: In addition to indicating the feasibility of reduced voltage tDCS, we propose an extra-low voltage "Limited Total Energy" approach where stimulation is continued at voltage compliance allowing time for impedance to decrease and target current to be reached.
Significance: Reduced-voltage and Limited Total Energy tDCS are viable approaches towards more protective and robust tDCS protocols.

1. Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that is being evaluated for the treatment of depression, epilepsy, pain, facilitating stroke rehabilitation and further neurological conditions (Hummel et al., 2005; Fregni et al., 2006; Nitsche et al., 2008, 2009; Nitsche and Paulus, 2009). During tDCS, a weak constant current is passed across the brain using electrodes placed on the scalp; prolonged passage of current (e.g. >10 min) can lead to lasting changes in neuronal excitability (Nitsche and Paulus, 2000, 2001). Most commonly, conductive rubber pads wrapped in saline-soaked sponge pockets are used as tDCS electrodes.

Stimulation protocols for tDCS consist of a fade-in phase in which current is ramped up to the desired intensity (typically <30 s), the main stimulation phase at target intensity (typically 1–2.5 mA, for

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10–20 min), and a fade-out phase. The voltage needed to ramp up current and maintain stimulation depends on the impedance across the body and the electrodes. Skin (scalp), skull, CSF, and brain tissue contribute to body impedance, with skin impedance known to change depending on current intensity and density and stimulation duration (Kalia and Guy, 1995; Prausnitz, 1996). Electrode impedance is a function of dynamic electrochemical processes and is also a complex function of stimulation waveform and time (Prausnitz, 1996; Merrill et al., 2005; Minhas et al., 2010). It is precisely because tissue and electrode impedance across subjects and time is highly variable, that current controlled stimulation is used to ensure reproducible delivery of stimulation dose to the brain.

During tDCS, the voltage is therefore adjusted to maintain the desired current level across variable impedances. Poor electrode design and preparation can thus lead to higher voltages being applied. Although current/charge density and total delivered charge are considered the main parameters causing tissue damage and painful sensation (McCreery et al., 1990; Nitsche et al., 2003; Liebetanz et al., 2009), unnecessarily high voltages are also undesirable for several reasons. For example, as electrode voltage increases, additional electrochemical reactions are triggered (Merrill et al., 2005) leading to potentially undesired chemical products and pH changes (Minhas et al., 2010). In addition, with improperly designed stimulation electronics (e.g. using off-label iontophoresis devices), a sudden drop in impedance can lead to a surge in current. Joule heating leading to temperature increases is a function of both current and voltage, though is likely not significant during conventional tDCS or High-Definition tDCS (Datta et al., 2009).

As it may play a role in painful skin sensation and irritation, it seems worthwhile to limit the electrical potential applied to subject's scalps. Current tDCS devices are limited to output voltages of 20–43 V, independent of current applied (Iontophoresis devices can reach >90 V). Anecdotal evidence suggests that in some subjects the maximum voltage of the stimulator is reached (either software or hardware limited "compliance voltage") leading to stimulation being aborted. The goal of this short study was to determine lowest possible voltage limits for tDCS devices for 1.5 mA and 2.5 mA target currents using a common electrode design and montage. Experimentally and with a 4th order linear circuit model, we demonstrate that the decrease in impedance produced by the passage of current itself significantly reduces the compliance voltage required. Furthermore, recognizing that reaching and maintaining the target current intensity does not require a strictly controlled (linear) ramp, we develop a "Limited Total Energy" (LTE) approach to tDCS which allows robust extra-low voltage stimulation.

2. Methods

This study was approved by the IRB of the City College of New York. All seven subjects gave written informed consent.

tDCS was administered for 6 min (30 s ramp-up, 5 min stimulation, 30 s ramp-down) to seven healthy adult subjects, using a custom-designed battery-run circuit (Soterix Medical Inc., NY) which allows free adjustment of maximum output voltage and current magnitude. Current was ramped up and down linearly over 30 s. Two rubber electrodes wrapped in saline soaked sponges, one over the primary motor cortex and the other superior to contralateral orbit (Fig. 1a and b), were held in position by rubber elastic straps or tDCS head-gear. Stimulation was conducted with current magnitudes of 1.5 mA (with a maximum output voltage of 14.5 V) and 2.5 mA (with a maximum output voltage of 18.5 V). Voltage limits were selected based on pilot experiments. Electrode polarity was alternated such that subjects received both polarities for each stimulation intensity, but not all subjects participated in all trials. Voltage and impedance were independent of electrode polarity such that polarity results are pooled. No subject received more than four stimulations (anodal/cathodal, 1.5/2.5 mA), with at least a 24 h interval in between experiments.

Rubber electrodes were wrapped in saline soaked sponge pads (35 cm^2, Soterix Medical Inc. EasyPAD). Initially, sponge pads were moistened with 10 ml of 0.9% concentrated saline. The impedance across electrodes was measured 1 min before and after stimulation by injecting three currents (I = 50 μA, 100 μA, 150–200 μA) and recording the required potential. Stimulation was not started unless the initial impedance was $\leqslant$50 kΩ (I = 50 μA). In order to decrease impedance, the necessary amount of saline was added to the sponge pads and soft pressure was applied to ensure uniform contact and wetting of the hair and scalp. Care was taken to minimize excessive wetting and dripping across the scalp. During stimulation, voltage and current across electrodes were recorded every 10 s. Subjects were asked to rate their skin sensation on a subjective scale of 0–10 and give a qualitative description (itching, burning, tingling...) of the perceived sensation every minute during and 1 min before and after tDCS.

Pre-tDCS and post-tDCS (in each test current group: n = 10 for 2.5 mA; n = 8 for 1.5 mA) impedance values were paired and divided. Kolmogorov–Smirnov tests did not indicate that the different measurement-current groups' came from different distributions, so these groups were pooled together. The resulting two sample sets of ratios (1.5 mA and 2.5 mA) were each tested for difference with unity using two-sided t-tests. The difference between the two sample sets of ratios was also tested for significance using a two-sided unpaired t-test with $p \leqslant 0.01$ considered significant (Fig. 1c). A Bonferroni multiple comparison correction for three comparisons was also performed and did not affect significance.

Motivated by analog circuit models of human tissue impedances in the literature (Panescu et al., 1994; Lafargue et al., 2002; Kuhn et al., 2009), we used least squares linear regression to fit models of R, RC, and RLC series circuits to the recorded voltage and current data for the averages of the 1.5 mA and 2.5 mA trials. While the RLC series interconnection captured the behavior more closely than any of the circuits, it still did not appear qualitatively correct, so we also tried higher order models. Using the Akaike criterion for model fit (Akaike, 1973), extended to short data sequences (Sugiura, 1978) which makes a trade-off of maximizing model accuracy and minimizing model complexity, we picked a best fitting (in a least-squares sense) model of the form:

$$V(t) = C_1 + C_2 I(t) + C_3 \frac{dI(t)}{dt} + C_4 \int I(t)dt + C_5 \int\int I(t)dtdt \qquad (1)$$

which captured all of the qualitative behavior of the data (Fig. 1d and e). Under the assumption that unaccounted-for nonlinearities in the system would cause the 1.5 mA data to be different in character from the 2.5 mA data, we initially analyzed the two data sets separately. However, after comparing the parameters (C_1, C_2, C_3, C_4, C_5) fit for each of the ten 1.5 mA trials vs. the parameters fit for each of the eight 2.5 mA trials, we found no significant differences (2-sided unpaired t-test, corrected for multiple comparisons-one for each coefficient), and thus cannot discard the null hypothesis that the system is well approximated by a single 4th order linear system of the above form, with C_1–C_5 = 3.99; 3.64; 1.395; −0.00992; 0.0000335, for all 1.5 mA and 2.5 mA trials.

3. Results

Impedance across electrodes was monitored before, during, and after tDCS. Pre- and post-tDCS impedance values differed significantly (Fig. 1c). Prior to stimulation the average impedance was 39.4 kΩ ± 8.9 (I = 50 μA), 32.1 kΩ ± 5.1 (I = 100 μA), and 23.7 kΩ ± 4.6 (I = 150–200 μA). As tDCS was initiated, impedance decreased significantly, approaching a minimum value after ~30 s

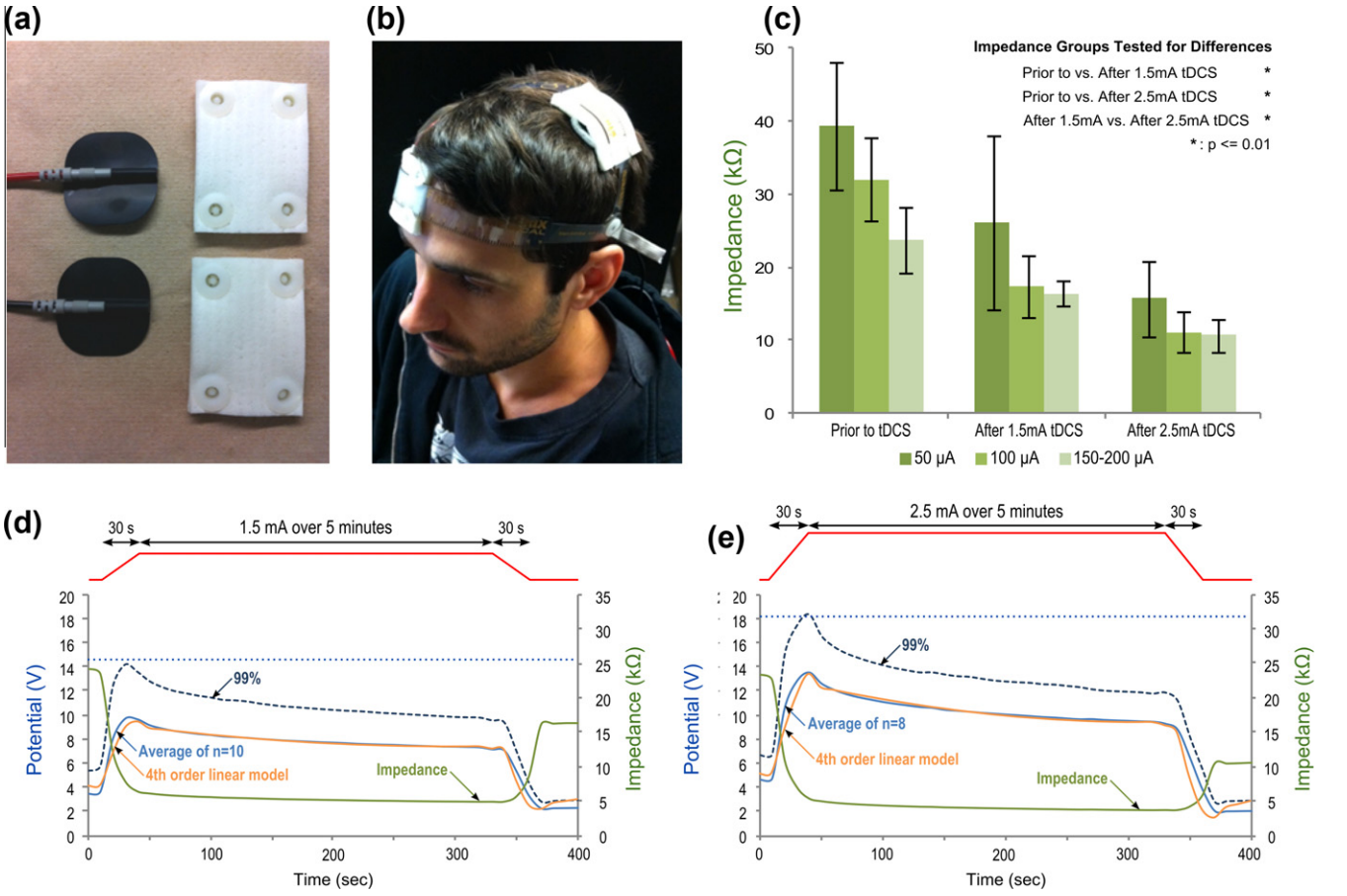

Fig. 1. tDCS Set-up, impedance, and voltage required during stimulation. Conductive rubber pads and saline soaked sponge-pockets used in this study (a); Head-gear for positioning electrode on the scalp. Electrode montage C_3–SO (b); Impedance across electrodes prior to and after 1.5 mA and 2.5 mA tDCS, pooled impedance group comparisons (*indicates significance) (c); Average voltage (blue) and impedance (green), top 99th percentile voltage interval (dashed line) and approximation of 4th order linear model (orange) during course of stimulation for 1.5 mA and 2.5 mA tDCS (d and e). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(corresponding to the ramp up duration where target current is achieved). Average impedance continued to decrease incrementally over several minutes during tDCS (Fig. 1d and e). During tDCS, after 3 min of stimulation, average impedance was 5.1 kΩ ± 0.7 (I = 1.5 mA) and 4.0 kΩ ± 0.5 (I = 2.5 mA). After 2.5 mA and 1.5 mA stimulation was completed, average impedance was 15.8 kΩ ± 5.1 (I = 50 µA) and 26.2 kΩ ± 12.0 (I = 50 µA) respectively, in both cases lower than pre-stimulation values. Using 2.5 mA of stimulation both during tDCS impedance and post-tDCS impedance was significantly lower compared to 1.5 mA stimulation (Fig. 1c).

A voltage peak during current ramp-up reflects the high initial barrier skin impedance, whereas after the current is ramped up to the desired magnitude, stimulation can be maintained with a gradually lower voltage level, due to asymptotically dropping skin impedance. The voltage required to produce the ramp and target current was monitored during tDCS (Fig. 1d and e). As expected, voltage increased as current ramped up reaching a maximum of 9.63 V ± 2.13 (I = 1.5 mA) and 13.44 V ± 2.25 (I = 2.5 mA). In no subject was the maximum stimulator voltage reached. Assuming a normal distribution, statistical analysis indicated that for the top 99th percentile voltage peaks of 14.1 V (I = 1.5 mA) and 18.3 V (I = 2.5 mA) would be expected. Voltage decreased incrementally during tDCS, corresponding to the associated impedance decrease.

A linear model was developed to predict impedance changes during tDCS using the above data. Though lumped-parameter circuit models have been proposed (representing skin tissue layers etc.), including non-linear elements, we parameterized an empirical model with the goal of specifically reproducing voltage requirements during tDCS as a *single linear* system. We found performance is well approximated by a single 4th order model (C_1–C_5 = 3.99; 3.64; 1.395; −0.00992; 0.0000335; Eq. (1)) providing a basis for designing optimized protocols (e.g. minimal voltage, sensation…), as well as real time adaptive stimulation. Consistent with previous reports (Dundas et al., 2007), subjects never reported more than moderate tingling, itching or slight burning skin sensation during or after stimulation, with average subjective ratings (scale 0:10) of 1.23 ± 0.45 (1.5 mA) and 1.71 ± 0.53 (2.5 mA) during tDCS (5 min) and peak ratings of 2.48 ± 0.69 (1.5 mA) and 3.19 ± 0.75 (2.5 mA).

Though pre-stimulation resistance is evidently grossly indicative of a faulty electrode set-up (e.g. dry sponges, unconnected cables), for the electrodes and set-up criteria used here (⩽50 kΩ at I = 50 µA) we observed no correlation between pre-stimulation resistance and subjective sensation at 1.5 mA or 2.5 mA.

4. Discussion

Our results indicate that using conventional electrode montages (e.g. C_3–SO, C_3–C_4), and appropriate electrode types and preparation (e.g. impedance checks), the voltage limits of clinical tDCS devices can be decreased to values <20 V. Specifically, in a current target specific manner, for 1.5 mA stimulation, output voltage of the device can be limited to 14.5 V, whereas 18.5 V is sufficient for successful stimulation at 2.5 mA target current intensity. Using

smaller electrodes (Nitsche et al., 2007; Minhas et al., 2010), lower-salinity electrodes (Dundas et al., 2007), or increased electrode separation (e.g. extracephalic montages) is expected to increase voltage demands. We describe a holistic approach to tDCS technology that contrasts with the current methods of strict current ramps and generic voltage limits. This approach can combine: (1) pre-stimulation impedance thresholds (which indicate set-up conditions); (2) statistical methods; (3) Limited Total Energy (LTE); and (4) linear models and feed-back control. We consider how these approaches can increase the robustness and safety of tDCS.

4.1. Statistical methods for reduced voltage tDCS – limitations

We show that for a given tDCS configuration (electrode type, size, and montage) maximal voltage excursions can be empirically determined – and models can be developed and parameterized to predict average performance. Statistical methods can then be used to consider required voltage compliance (e.g. for 99% of subjects) for a given protocol (Fig. 1d and e), but outliers are expected (e.g. 1%). One can therefore further increase stimulator voltage (which raises safety concerns and ignores a potential faulty set-up), abort stimulation in such cases (which is particularly onerous in prolonged clinical trials or patient treatment), or consider the further approaches discussed next.

4.2. Leveraging current and time dependent impedance decrease through tDCS-LTE

Notable qualitative features of impedance during tDCS are the rapid (seconds) decrease in impedance during the initial phase of tDCS and further gradual (minutes) decrease in impedance with stimulation time. This rapid response is likely based on decreased impedance with increased current (also evident even at low intensities during pre-stimulation impedance monitoring; (Fig. 1c) and appears to reverse after stimulation. Due to this rapid impedance decrease, increasing current intensity does not increase voltage demands to the same extent. For example, note that given a typical starting impedance 40 kΩ (measured with $I = 50\ \mu A$), with no changes in impedance, a compliance voltage of 60 V would be required at 2.5 mA. The gradual decrease appears to account for the lasting (post-stimulation) change in impedance, and is likely mediated by skin changes (Kalia and Guy, 1995) while electrochemical changes at the electrode might increase impedance (Merrill et al., 2005).

Though resistance (and related voltage) excursions during tDCS vary across subjects, the decrease in impedance is typical, and thus leveraged for robust extra-low voltage tDCS using the Limited Total Energy (LTE) approach-even in cases where high impedance is initially encountered. At the initiation of tDCS, impedance is relatively high such that the voltage limit is approached or even reached at the end of the ramp-up period, but impedance starts to decrease, reducing voltage demands. If a stimulator is designed to *not* automatically abort tDCS when the voltage threshold is reached, but rather hold the target voltage, then within seconds the voltage demand will decrease. This concept of tDCS-LTE alongside other approaches is illustrated in Fig. 2. tDCS-LTE is the only approach that combines voltage limitation with limitations on current ramp-rate and control of target current during the main phase.

4.3. Optimization of tDCS – waveform metrics and tDCS-LTE

Generally, how should tDCS be optimized for safety and efficacy? We can assume that the behavioral/therapeutic effects of tDCS are mediated by the current (which determines brain electric

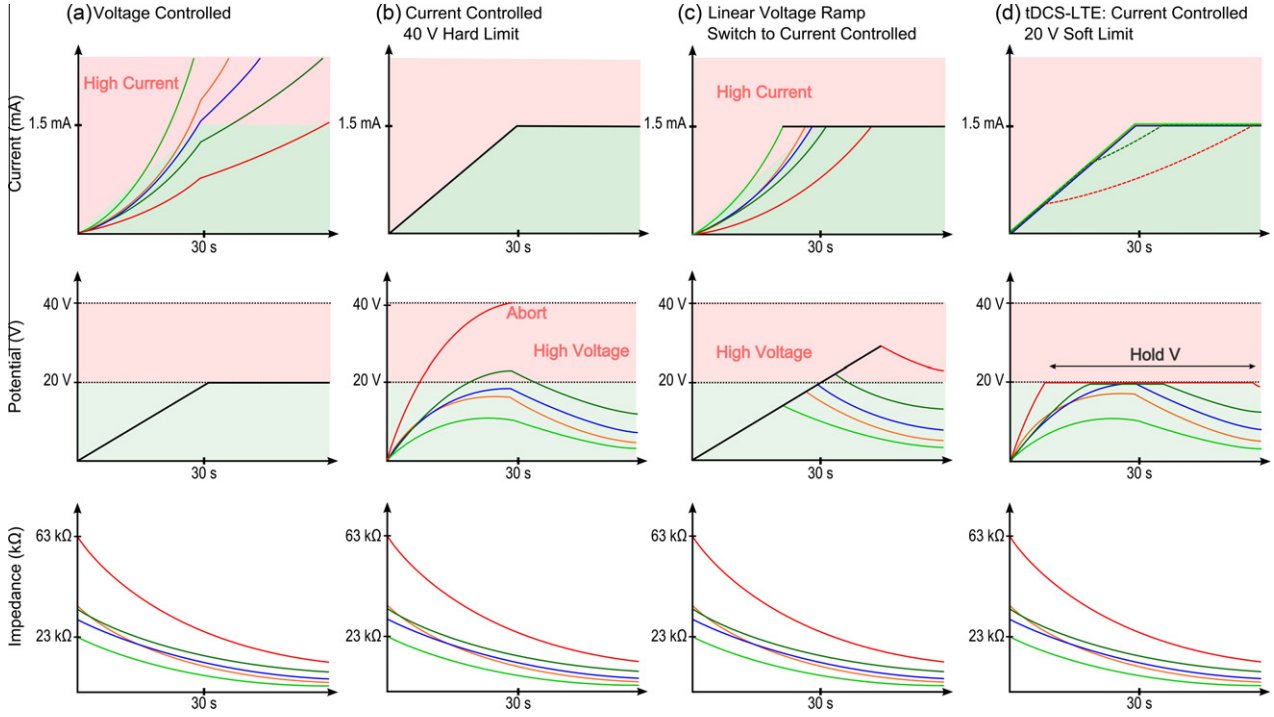

Fig. 2. Comparison of four approaches to control during tDCS. Schematically shown are the course of current and voltage according to four impedance profiles: (a) Voltage controlled, where the voltage is ramped up to a target with no control consideration of current. This approach limits neither the rate of current increase nor the target current. Voltage control is unsuitable for tDCS. (b) Conventional current controlled with high voltage limit, where current is controlled and voltage is allowed to increase until a "hard limit" where stimulation is suddenly aborted. This approach is common in tDCS. (c) Voltage ramp with switch to current control, where voltage is ramped up until a target current is reached at which point current is maintained at the target level. This approach limits target current but not the rate of current increase. (d) Limited the rate of current increase and can achieve target current with minimal voltage. Total energy, where current is limited to a linear ramp to target, but can decrease transiently below target levels as impedance decrease. This approach limits the rate of current increase and can achieve target current with minimal voltage.

fields, not voltage) and specifically the "tonic" phase of tDCS (lasting minutes), not the transient ramp up or ramp down. Moreover, we consider the common side-effects of tDCS associated with effects at the skin (e.g. prickling) and linked to electrochemical reactions at the electrode. Control of electrochemical reactions is accomplished through selection of electrode materials and electrolytes (saline, gel; considered in Merrill et al., 2005; Dundas et al., 2007; Minhas et al., 2010) and limitations on stimulation waveform metrics, which we consider here. Waveform metrics can include any combination of: (1) total applied charge, average charge density (charge/electrode area), or peak charge density (at electrode edges) – tDCS is evidently not charge balanced; (2) instant power or energy, which effects heating as well as battery consumption; (3) voltage, which limits which electrochemical reactions will initiate-though care must be taken to distinguish total cell voltage for electrode interface voltage (Merrill et al., 2005). Though these processes are complex and strict safety guidelines have yet to be established, a rational goal is to minimize charge, power, and voltage while not interfering with current delivery in the tonic phase. Additional constraints include: (4) robustness of device use, including anticipating non-ideal setup or changes (e.g. motion) during stimulation; (5) reducing total stimulation time, for convenience; (6) minimizing sensation, which effects tolerability and reliability of sham in clinical trials; and (7) avoiding trials that are aborted, for example if a strict compliance voltage is reached.

Maximum ramp slope is limited by the sensation associated with sudden current changes, and is conventionally 10–30 s to target, based on empirical experience. Further decreasing ramp slope (increasing ramp up time by T_r s) may decrease required compliance voltage, but at the cost of total stimulation time ($+T_r$; Seconds), charge ($+0.5T_r{}^{*}TargetCurrent$; Coulombs), and energy ($+0.33T_r{}^{*}Resistance{}^{*}TargetCurrent^2$; Watts, assuming fixed resistance). Empirical studies and statistical approaches can optimize ramp slope, but if one maintains a strict voltage compliance limit, a trade-off ensues between (1) decreasing ramp slope to accommodate an increasingly smaller percentage of high-resistance outlier subjects; (2) limited ramp time, but aborting stimulation when the compliance voltage is reached, even briefly, in outlier subjects.

tDCS Limited Total Energy (tDCS-LTE) can be combined with any ramp slope and target current allowing: (1) operation under reduced compliance voltage; and hence (2) reduced maximum instant power; (3) total time remains fixed compared to strict current control; (4) charge is fixed or reduced (since current never exceeds the ideal trace); and (5) for a given ramp slope and target current, if one adopts the lowest feasible voltage (still allowing target current to be achieved) then energy is minimized; (6) sensation will be comparable or reduced compared to strict current control since the electrochemical burden is reduced; (7) in addition, though the relationship between voltage and sensation is not trivial (Dundas et al., 2007; Minhas et al., 2010) this approach allows for resistance accommodation in high-resistance subjects, which may otherwise experience higher transient sensation. tDCS-LTE is thus consistent with the general objectives of safe and robust design outlined above.

The trade-offs of using tDCS-LTE is that in the some subjects, the current will not reach target within the ideal ramp time but importantly: (A) as the compliance voltage is statistically set, delays occur only in the minority of subjects (e.g. 1%) where the stimulation would otherwise be aborted; and (B) the situation where current does not reach target for the majority of the tonic phase is *not* expected because of the rapid resistance drop – rather in such cases there is likely a faulty set-up and the limitation of current applied by tDCS-LTE thus protective. Moreover, it is straightforward to equip the device to monitor/indicate when LTE is active which may trigger corrective action by the operator, for example checks of sponge saturation. tDCS-LTE is not proposed as an alternative to other approaches to increase stimulation safety, robustness, or tolerability (e.g. electrode design), but as an adjunct.

4.4. Impedance monitoring before and during stimulation – model based optimization

Pre-stimulation impedance provides information on the quality of electrode set-up in each subject. Anecdotal reports suggest that in those subjects in whom it is challenging to obtain a low pre-stimulation resistance, conventional stimulators abort due to compliance voltage. Pre-stimulation impedance therefore may be useful as a target threshold during set-up, but in subjects where surface conditions (skin/hair) result in unavoidable high pre-stimulation resistance, LTE may be a requirement.

Sophisticated models of both tissue (skin) and electrode impedance have been developed (Panescu et al., 1994; Lafargue et al., 2002; Kuhn et al., 2009); our approach was particular in that we restricted the model to a linear system, while recognizing the non-linear nature of the underlying biophysics. We thus developed a single linear model to predict impedance changes during tDCS, which can surely be expanded on, but which establishes the principle. Rather than a priori assumptions about underlying biophysics and lumped-parameter circuit equivalents, we proposed an automatic model development method. We expect impedance behavior will be electrode material and montage dependent, and this approach can be extended to accommodate additional data sets. The model results are not trivial, including current and time dependent impedance decreases, which can be readily leveraged in stimulation optimization without necessarily isolating a biophysical substrate.

Specifically, towards more intelligent tDCS protocols, the linearity of the model will allow optimized stimulation through: (1) a priori prediction of compliance voltages for tDCS protocols, including based on target current and ramp time constraints; with (2) further allowances for LTE approaches; plus (3) implementations of real-time control algorithms (tissue impedance was observed to vary across subjects and within subjects over days, so most likely a feedback control approach would have superior robustness and performance). For example, information of sensation sensitivity to voltage and current change rate can be used to reduce discomfort during stimulation as well as enhance sham protocols. In addition, intelligently optimized protocols can be applied for susceptible populations, such as children or subjects with brain lesions (Datta et al., 2011) or skull defects (Datta et al., 2010).

In summary, this study demonstrates statistical approaches to reduced-voltage tDCS, where stimulator voltage is limited based on the target current. Combined with tDCS-LTE, this approach allows for reduced voltage stimulation. Model-based adaptive approaches may provide additional customization. Though tDCS using existing stimulators is generally well tolerated (Nitsche et al., 2003; Poreisz et al., 2007), tDCS-LTE provides further automatic robustness that may be especially useful in vulnerable populations (e.g. pediatric), challenging deployment environments (e.g. where other factors limit electrode design), or large scale clinical trials.

5. Conflict of Interest

The City University of New York has patent applications on brain stimulation with Christoph Hahn, Justin Rice, Preet Minhas and Marom Bikson as inventors. Marom Bikson is co-founder of Soterix Medical Inc.

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