NeuroRehabilitation 36 (2015) 115–126
DOI:10.3233/NRE-141199
IOS Press

Feasibility of using high-definition transcranial direct current stimulation (HD-tDCS) to enhance treatment outcomes in persons with aphasia

Jessica Richardson[a,*], Abhishek Datta[b], Jacek Dmochowski[c], Lucas C. Parra[c] and Julius Fridriksson[a]
[a]*Department of Communication Sciences & Disorders, The University of South Carolina, Columbia, SC, USA*
[b]*Soterix Medical, Inc., New York, NY, USA*
[c]*Department of Biomedical Engineering, The City College of New York of CUNY, New York, NY, USA*

Abstract.
BACKGROUND: Transcranial direct current stimulation (tDCS) enhances treatment outcomes post-stroke. Feasibility and tolerability of high-definition (HD) tDCS (a technique that increases current focality and intensity) for consecutive weekdays as an adjuvant to behavioral treatment in a clinical population has not been demonstrated.
OBJECTIVE: To determine HD-tDCS feasibility outcomes: 1) ability to implement study as designed, 2) acceptability of repeated HD-tDCS administration to patients, and 3) preliminary efficacy.
METHODS: Eight patients with chronic post-stroke aphasia participated in a randomized crossover trial with two arms: conventional sponge-based (CS) tDCS and HD-tDCS. Computerized anomia treatment was administered for five consecutive days during each treatment arm.
RESULTS: Individualized modeling/targeting procedures and an 8-channel HD-tDCS device were developed. CS-tDCS and HD-tDCS were comparable in terms of implementation, acceptability, and outcomes. Naming accuracy and response time improved for both stimulation conditions. Change in accuracy of trained items was numerically higher (but not statistically significant) for HD-tDCS compared to CS-tDCS for most patients.
CONCLUSIONS: Regarding feasibility, HD-tDCS treatment studies can be implemented when designed similarly to documented CS-tDCS studies. HD-tDCS is likely to be acceptable to patients and clinicians. Preliminary efficacy data suggest that HD-tDCS effects, using only 4 electrodes, are at least comparable to CS-tDCS.

Keywords: Aphasia, feasibility, high-definition tDCS, stroke, tDCS, treatment outcomes

1. Introduction

Increasing evidence suggests noninvasive brain stimulation can induce lasting functional changes in the central nervous system (Fregni & Pascual-Leone, 2007; Hummel & Cohen, 2005; Schulz, Gerloff, & Hummel, 2013). Of particular interest is transcranial direct current stimulation (tDCS) due to its ease-of-use, low risk, and potential clinical application for a variety of disorders. tDCS has been shown to boost learning outcomes for cognitive skills (e.g., Cerruti & Schlaug, 2009; Cohen Kadosh et al., 2010; Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Harty et al., 2014)

*Address for correspondence: Jessica Richardson, Ph.D., CCC-SLP, Assistant Professor, Department of Communication Sciences & Disorders, The University of South Carolina, Columbia, SC 29208, USA. Tel.: +1 803 777 5049; Fax: +1 803 777 3081; E-mail: j.d.richardson@sc.edu.

and enhance treatment outcomes in post-stroke populations (e.g., Bastani & Jaberzadeh, 2012; Yang et al., 2012; Holland & Crinion, 2012; Lee & Chun, 2014). The results are often compelling; for instance, Lindenberg, Renga, Zhu, Nair, and Schlaug (2010) reported a threefold increase in learning performance on a dexterity task when physical/occupational therapy was paired with tDCS (versus sham). Combining the results of studies with persons with aphasia (PWAs), tDCS has been shown to enhance outcomes by 25% (compared to sham stimulation), with effects persisting for up to three weeks (Holland & Crinion, 2012). The underlying mechanisms of tDCS modulation are not well understood but emerging evidence points to NMDA- and BDNF-mediated plasticity (Fritsch et al., 2010; Nitsche et al., 2004; Stagg et al., 2009).

Behavioral changes and therapeutic enhancement following tDCS administration depend on which cortical areas are targeted; careful positioning of both active and reference electrodes is crucial (Mendonca et al., 2011; Moliadze, Antal, & Paulus, 2010; Nitsche & Paulus, 2000). Mendonca et al. (2011) demonstrated the importance of electrode placement when one montage did not lead to any observed clinical effects compared to the other montage under study. Modeling of current flow for the ineffective montage revealed that the peak electrical field occurred in the temporoparietal cortex and not over the motor cortex (as intended with intuitive positioning). This study highlights an important emerging theme in tDCS – intuitively positioning the active electrode over the intended cortical area and placing the reference electrode at a location used in previous research (e.g., contralateral forehead) does not ensure maximal current flow directly under the active sponge. The location of 'hot-spots' (local maxima) cannot be readily predicted without careful modeling of precise anatomy and tissue conductivity (Datta et al., 2009; Datta, Truong, Minhas, Parra, & Bikson, 2012; Park, Hong, Kim, Suh, & Im, 2011).

This problem is compounded in chronic stroke, where large cerebrospinal fluid-filled lesions may drastically alter current flow and serve as an attractor for current, even when electrodes are placed on an area of the scalp away from the lesion (Datta, Baker, Bikson, Fridriksson, 2011). Without solving this problem, the full potential of tDCS as an adjuvant to therapy in stroke populations may be unrealized due to insufficient individualization. Advances in computational models of current flow in individualized and detailed anatomical models derived from MRI are underway (Dmochowski, Datta, Bikson, Su, & Parra, 2011) and development of a technique thought to increase current focality is in progress. This technique, called high-definition tDCS (HD-tDCS) uses gel-based electrodes similar to those used in electroencephalography (EEG) (Minhas, 2010). Sensations similar to those reported by Poreisz, Boros, Antal, & Paulus (2007) for conventional sponge-based tDCS (CS-tDCS) have been reported for HD-tDCS (Borckardt et al., 2012; Patel et al., 2009). Recently, Borckardt and colleagues (2012) demonstrated low ratings for pain and unpleasantness during HD-tDCS. Ratings decreased over time, and participants were not able to guess (above chance) which condition was active versus sham. Additional studies have directly demonstrated the physiological effects on motor cortex excitability (Caparelli-Daquer et al., 2012; Kuo et al., 2013). Kuo et al. (2012) observed larger and longer-lasting TMS-evoked MEP changes and potentially reduced skin sensations with HD-tDCS in comparison to CS-tDCS in a crossover design. However, unlike CS-tDCS, the tolerability of receiving HD-tDCS for consecutive weekdays as an adjuvant to behavioral treatment has yet to be demonstrated. Further, though HD-tDCS is thought to increase focality and field intensities at desired cortical targets, whether such an approach would result in comparable, better, or worse outcomes compared to CS-tDCS in stroke rehabilitation remains to be seen. Lastly, a portable clinician-friendly device that can deliver HD-tDCS, and methods for reliable session-to-session administration, do not yet exist.

An ideal population for tackling such issues is one where a clear target for stimulation can be identified. Patients with post-stroke aphasia may be such a population, as there is evidence that intact cortical areas adjacent to the stroke lesion (perilesional areas) mediate recovery (Fridriksson, 2010; Fridriksson, Richardson, Fillmore, & Cai, 2012). In a recent study, Fridriksson (2010) showed that aphasia recovery induced by intensive naming treatment was associated with functional brain changes in the damaged left hemisphere. Most recently Fridriksson et al. (2012) demonstrated that increased left hemisphere activation of perilesional cortex was not only correlated with anomia treatment outcome, but that baseline measures of activation in these areas were predictive of increased activation post-treatment. This suggests that fMRI during picture naming could potentially serve as a tool to define cortical targets for brain stimulation. fMRI has previously been used to identify cortical targets in two tDCS studies that revealed that anodal tDCS enhances the effect of a computerized aphasia treatment

in chronic stroke by increasing naming accuracy (Baker, Rorden, & Fridriksson, 2010) and decreasing naming response time (Fridriksson, Richardson, Baker, & Rorden, 2011). However, these promising studies utilized CS-tDCS, making it difficult to decipher whether tDCS directly targeted intended cortical areas.

For the current study, we automated techniques required for individualized modeling and targeting (i.e., peak electrical field delivered to intended cortical area; Dmochowski et al., 2013; Huang et al., 2012) and sought to demonstrate the feasibility of targeting in clinical practice. We also developed a HD-tDCS device that could be operated in a clinical setting and/or in patient homes in a manner similar to CS-tDCS devices. Finally, in eight patients with chronic aphasia, we administered both CS-tDCS, at a dosage well-tolerated by patients that has proven to enhance outcomes (Baker et al., 2010; Fridriksson et al., 2011) and HD-tDCS, at a dosage expected to result in comparable sensations to CS-tDCS but with increased focality and intensity (Kuo et al., 2013). We sought to determine feasibility outcomes, specifically the ability to implement the study as designed, the acceptability of repeated administration of HD-tDCS to patients, and preliminary efficacy to determine if behavioral outcomes of aphasia treatment administered concomitantly with HD- tDCS were comparable to those achieved via CS-tDCS.

2. Methods

2.1. Patients

The study was approved by the University of South Carolina's Institutional Review Board. Eight patients (four female) with chronic stroke-induced aphasia, aged 51- to 74-years ($M = 60.63$; $SD = 8.88$), participated in the current study (Table 1). Range of time post-stroke onset was 9 to 312 months ($M = 100.25$; $SD = 91.98$). Aphasia assessment using the Western Aphasia Battery-Revised (WAB-R; Kertesz, 2007) classified five patients as having Broca's aphasia and three patients as having anomic aphasia. WAB-R Aphasia Quotient (AQ) scores (a measure of severity) ranged from 43.4 to 92 ($M = 74.4$; $SD = 15$). Patients were required to temporarily discontinue participation in other speech-language treatment interventions (except support groups) until study completion.

2.2. Study design

Four patients received CS-tDCS during the first phase and then crossed-over to HD-tDCS during the second phase following a one-week rest period (Fig. 1). The remaining four patients received the opposite treatment order. Computerized anomia treatment coupled with brain stimulation was administered for five consecutive days during each treatment period. Blood pressure, heart rate, and discomfort ratings (using the Wong-Baker FACES Pain Rating Scale) were measured before and after each session.

Total study duration was five weeks. Patients were assessed at 12 different time points throughout the experiment: twice at Phase 1 baseline (P1-B), twice immediately post the final treatment session (P1-IP), twice at one week follow-up (P1-FU), twice at P2-B, twice at P2-IP, and twice at P2-FU. The mean of the two sessions at each critical time point (i.e., B, IP, FU) was calculated and used for data analysis. After each patient completed all assessment and treatment sessions (22 total sessions), assessment measures were scored by trained judges blinded to treatment condition.

2.3. fMRI task and procedure

High-resolution T1- and T2- MRI scans and fMRI results associated with a language task were utilized in

Table 1
Patient characteristics

	Sex	Age (years)	Post-Onset (months)	Aphasia Type	WAB-R AQ‡	Lesion Size (cc)	Target Coordinates (x,y,z; MNI)
P1	F	58	312	Anomic	86.2	34.99	−64, −28, 6
P2	F	51	79	Broca's	73.5	229.12	−50, −52, 18
P3	M	64	104	Broca's	68.1	130.47	−52, −42, 12
P4	M	67	76	Broca's	73.5	252.38	−58, −36, 4
P5	F	48	109	Broca's	43.4	116.71	−60, −26, −2
P6	F	74	80	Anomic	92	78.03	−64, −32, −4
P7	M	56	33	Broca's	72.7	191.58	−48, −42, −8
P8	M	67	9	Anomic	85.4	39.22	−62, −12, −4

Abbreviation: WAB-R AQ, Western Aphasia Battery-Revised Aphasia Quotient; MNI, Montreal Neurological Institute coordinates. ‡Maximum score of 100.

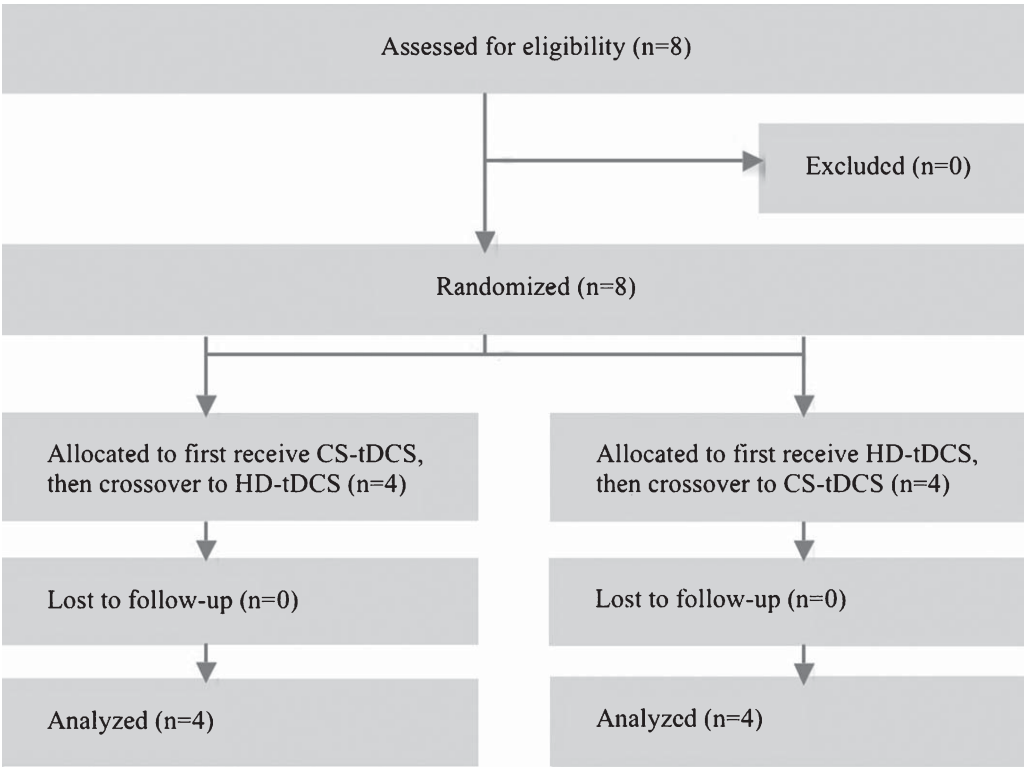

Fig. 1. Flow diagram of the study design.

order to determine electrode placement on a patient-by-patient basis. MRI data collection relied on a 3T Siemens Trio scanner (Erlangen, Germany). For details on the language task as well as the scanning parameters and data analyses, see Fridriksson (2010). The location of voxels with the highest Z-scores in the left perilesional cortex (defined as the cortex 3–15 mm beyond the lesion rim; Fridriksson et al., 2012) associated with correct naming for each patient is listed in Table 1. This location served as the target for both conditions.

2.4. Modeling and targeting

Individualized modeling and targeting procedures were developed for this project (Dmochowski et al., 2013; Huang et al., 2012). Briefly, the 1mm^3 resolution T1 and T2 scans were automatically segmented using SPM8 and a newly developed tissue probability map (TPM). This TPM is unique in that it covers the entire head (including neck) and represents 6 tissue types (skin, skull, air, CSF, gray matter, white matter). The resulting segmentation masks were automatically corrected to reduce small segmentation errors and smoothed to allow meshing for the purpose of finite element method (FEM) modeling. Virtual electrodes were automatically placed on 74 locations based on the 10/10 EEG system using standard landmarks (inion, nasion, peri-auricular points). Laplace equations were solved for all electrode locations using a commercial FEM solver (Abaqus). Targeting was performed in MATLAB using custom software (Dmochowski et al., 2011, 2013).

Targeting was performed with the goal of achieving maximum stimulation intensity at the target, with the constraint that total currents did not exceed 2 mA (and no more than 1 mA per electrode). The targeting revealed, in all instances, 2 anodes and 2 cathodes, each drawing 1 mA of current (see Fig. 2), with apparent differences in modeled current intensities at target when comparing the stimulation conditions. The HD-tDCS electrode locations varied across subjects as a result of drastically differing lesion anatomy and target location (Fig. 2, for more detail see Dmochowski et al., 2013).

2.5. Electrode positioning

CS-tDCS. Each patient was fitted with a swim cap prior to electrode positioning. Anatomical landmarks

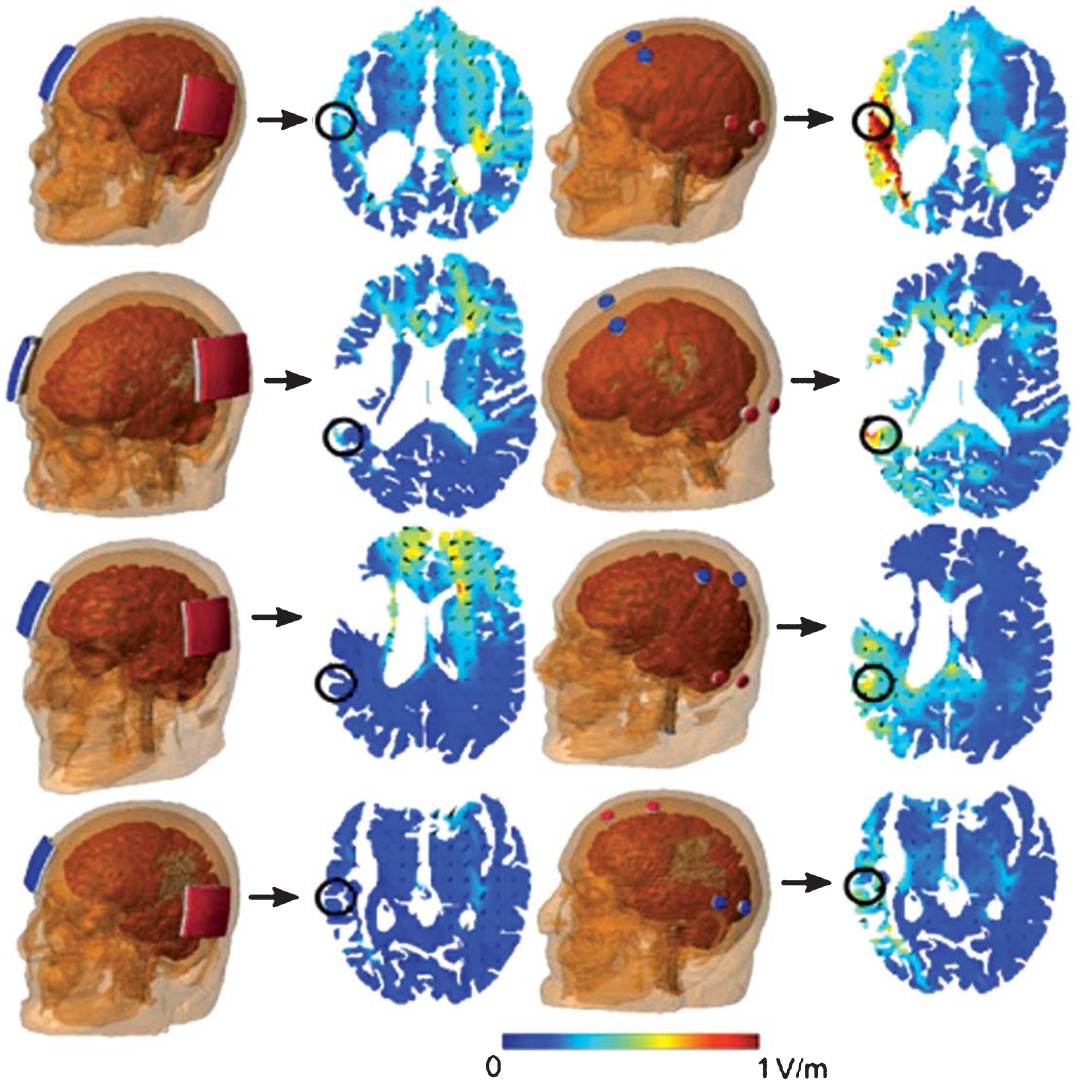

Fig. 2. Electric field solutions for conventional sponge (CS-tDCS) versus high-definition (HD-tDCS) for four sample subjects in the study. Patient-specific head models were built based on individual MRI, FEM modeled, and optimized to focus currents to an fMRI-determined target (open circle). HD-tDCS results in higher electrical field intensities at target compared to CS-tDCS.

were made on the cap to ensure consistent cap fitting and electrode placement during treatment. Using *MRIreg*, a computer program that registers a MRI scan with scalp locations, and a magnetic tracking system (*Flock of Birds,* Ascension Technology, Burlington, VT), the area on the scalp closest to target voxels (Table 1) was identified and marked on the swim cap. This cap was fitted on the patient prior to the start of each CS-tDCS session and, using the cap landmarks, marks were made directly on the scalp to indicate anode electrode placement. Caps were then removed and electrodes (with cathode placed supraorbitally) held in place with self-adhesive bandages.

HD-tDCS. A standard EEG cap was worn, with 10/10 standard electrode locations indicated (Fig. 3). Accurate placement of the cap relies on identifying the nasion, inion, and two peri-auricular points. The same approach of electrode placement was used also in the computational model to ensure accurate alignment. The electrode positions indicated by the modeling are listed in Table 1 and shown for a subset of patients in Fig. 2. Electrode insets were preloaded into the EEG cap at

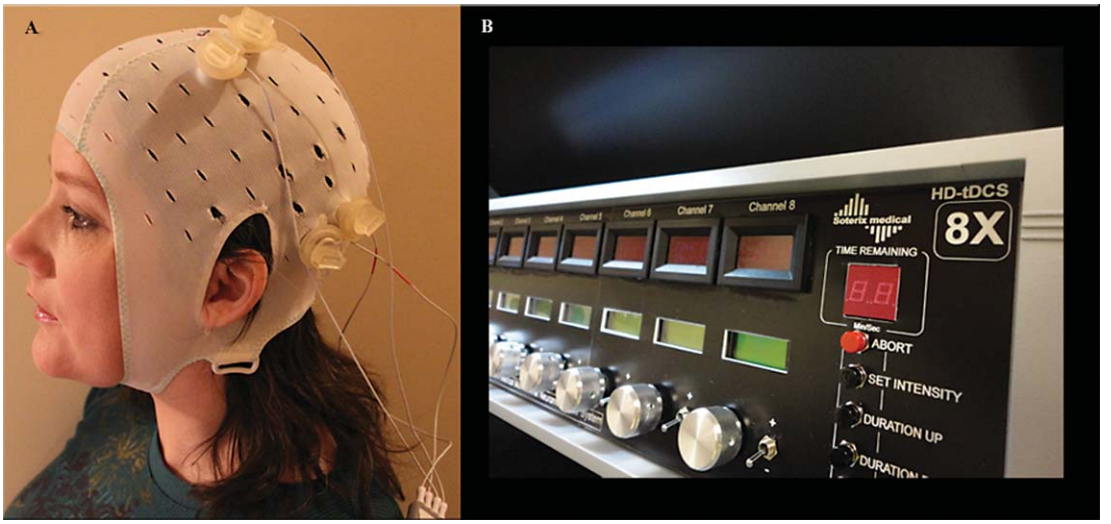

Fig. 3. A: High-definition tDCS (HD-tDCS) was applied using EEG sized electrodes held in plastic insets in an EEG cap. B: 8-channel HD-tDCS prototype device used in the study.

desired locations, and the cap was worn for the duration of the experiment (Fig. 3).

2.6. tDCS administration

CS-tDCS. Similar to previous studies performed by our group (Baker et al., 2010; Fridriksson et al., 2011), 1 mA was delivered for 20-min per session via two saline-soaked sponge electrodes (5×5 cm) and a constant current stimulator (MagStim Eldith DC stimulator, neuroConn, Ilmenau, Germany) placed out of the patients' sight.

HD-tDCS. A prototype was built to enable targeted stimulation (8x HD-tDCS, Soterix Medical, New York). The stimulator comprised of 8 independent, isolated channels, with a 9th electrode as a reference. The following controls to enhance subject safety/comfort were incorporated: 1) independent current control for each channel, and 2) maximum current limit/channel = ± 2 mA and maximum voltage = 35 V on each channel and on any combination of channels. For operator ease-of-use, current intensities for each channel could be easily adjusted with dials and independently monitored via bright backlit displays throughout experiment (Fig. 3). As with CS-tDCS, stimulation current ramped up and down linearly within 30 seconds at the beginning and end of the stimulation period. 1 mA per electrode (2 anodes, 2 cathodes) was delivered for 20-min per session via electrodes similar to those used in EEG.

2.7. Computerized treatment

The computerized treatment consisted of an audio-picture matching task similar to those used previously (Baker et al., 2010; Fridriksson et al., 2009, 2011). There were two word lists used (TrainedA and TrainedB; 50 words each) matched for syllable length, word frequency (Frances & Kucera, 1982), semantic category membership, and concreteness (Coltheart, 1981). Treatment included the following structure: 1) fixation, 2) audio stimulus, 3) picture stimulus, 4) response screen, and 5) feedback. (Brown noise was overlaid upon the audio stimulus to increase difficulty and improve attention to a task that can become monotonous.) Patients pressed large response buttons in the case of a match (green button) or non-match (red) between the audio and picture stimuli. Patients were provided a happy face picture (correct), a sad face picture (incorrect), or "no response" text as feedback. Each patient participated in 300 five-second trials per treatment session (randomly ordered), for 25 min total daily treatment. Half of the audio-picture pairs matched, while the other half did not. This computerized treatment occurred concurrently with tDCS, beginning 5 min prior to tDCS administration. The order of treatment lists per phase was randomized.

2.8. Preliminary efficacy assessment

Naming accuracy and response time of accurate naming was evaluated. Pictures (nouns) were consecutively

displayed on a laptop, with a 250 ms tone (300 Hz) at the beginning of each picture presentation. Patients were asked to overtly name each picture as soon as it was displayed. Trials ended following a response or after 10 s elapsed. AssessmentA included 50 pictures for TrainedA as well as an additional 20 pictures not targeted in treatment (UntrainedA). AssessmentB included 50 pictures for TrainedB and an additional 20 pictures not targeted in treatment (UntrainedB). UntrainedA and UntrainedB were matched lists included to assess generalization from treated to untreated nouns.

Naming assessment sessions were audio-recorded via Cool Edit Pro Version 2.0 (Syntrillium Software Corporation) and later scored by trained judges blinded to stimulation type, study phase, and trained/untrained status. Judges scored accuracy, making additional notations when patient responses were immediately correct (i.e., excluding self-corrections, fillers, circumlocutions). To determine change in accuracy, all accurate responses (i.e., correct or self-correct within 10 s of picture presentation) were included in statistical analysis. To determine change in response time, only responses that were immediately accurate were included in statistical analysis. Response time of these instances was assessed manually with Praat, measured from the onset of the pure tone to the initiation of the target word.

2.9. Analysis

Feasibility outcomes were addressed in the study, specifically 1) implementation, 2) acceptability, and 3) preliminary efficacy (Bowen et al., 2009; Conn, Algase, Rawl, Zerwic, & Wyman, 2010). Implementation analysis (1) examines the ease or difficulty of protocol delivery, comparison of CS- and HD-tDCS (time, portability, materials, etc.), clinician competency and reliability, and intervention integrity. Attrition, adherence, and adverse events are described to determine acceptability (2) of this protocol. Further, measurements of cardiovascular arousal and comfort were analyzed and compared. For preliminary efficacy estimates (3), tests were first conducted to confirm that effects similar to those observed in previous CS-tDCS studies were replicated, followed by a comparison of CS- and HD-tDCS outcomes. Friedman tests were conducted to determine the presence of differences in accuracy and response time of accurate naming of trained and untrained items between the 3 different treatment phases for both conditions. Follow-up pairwise comparisons were conducted using Wilcoxon Signed Ranks Test. Change in accuracy and response time was compared between CS-tDCS and HD-tDCS conditions using the Wilcoxon Signed Ranks Test. Sample size estimates for future studies were then performed.

3. Results

3.1. Implementation

The process of identifying and demarcating cortical targets (authors 1 and 5) and applying newly developed individualized modeling and targeting procedures (authors 2 through 4) lasted approximately 1 week per patient, with the majority of time devoted to manual correction of automated segmentation results (Dmochowski et al., 2013; Huang et al., 2012). The recruiting, scheduling, and protocol implementation was performed by a speech-language pathologist with brain stimulation research experience (author 1). HD-tDCS developers trained the clinician on device operation/troubleshooting, cap fitting, and electrode positioning.

One hour was allotted for each treatment session (unloading/setting up equipment, electrode placement, equipment testing, pre-treatment arousal/comfort assessment, impedance testing, instructions, treatment [25 min], post-treatment arousal/comfort assessment, and equipment break down/loading) and all treatment sessions (total = 80) were completed within the time allotment. Cleanup procedures for HD-tDCS were slightly longer than for CS-tDCS, since electrode insets, electrodes, and caps had to be washed and dried. Batteries for both devices were charged overnight. Accessories differed for CS- and HD-tDCS (e.g., swim caps and cohesive bandage vs. EEG caps, saline vs. Lanacane and signa gel, etc.). Despite the size difference between devices, portability was comparable.

3.2. Acceptability

Patients were recruited from those who had previously participated in functional neuroimaging research. Each patient completed 22 total sessions, conducted in a university clinic or their home, with no complaints, concerns, requests to discontinue participation, or adverse events. Heart rate and blood pressure remained unchanged during both treatments ($p > 0.1$, paired t-test). Patient ratings on the Wong-Baker FACES Pain Rating Scale for both CS- and HD-tDCS ranged

between 0 and 1 (out of 5). For CS-tDCS, a change in pre- to post-stimulation score (from 0 to 1) occurred only once; no changes in pre- to post-stimulation scores were noted for HD-tDCS. Sensations reported for CS-tDCS were itching, tingling, and burning; for HD-tDCS, tingling and burning.

3.3. Preliminary efficacy

See Table 2 for means and standard deviations for change in accuracy and response time of accurate naming. Friedman tests were conducted to see if there were significant differences in accuracy of trained and untrained items between each assessment point for each stimulation condition. The test was significant for trained items for CS-tDCS, $\chi^2(2,N=8)=12.45$, $p<0.01$, and HD-tDCS, $\chi^2(2,N=8)=9.87$, $p<0.01$, but not for untrained items ($p=0.96$, CS-tDCS, $p=0.25$, HD-tDCS). The same tests were conducted for response time of accurate naming, and were significant for trained and untrained items for CS-tDCS ($\chi^2(2,N=8)=12.25$, $p<0.01$, trained; $\chi^2(2,N=8)=12.00$, $p<0.01$, untrained) and HD-tDCS ($\chi^2(2,N=8)=13.00$, $p<0.01$, trained; $\chi^2(2,N=8)=7.00$, $p=0.03$, untrained). Follow-up pairwise comparisons (Wilcoxon tests) were conducted, and CS-tDCS significantly increased naming accuracy of trained items compared to baseline immediately post ($Z=-2.54$, $p=0.011$) and at follow-up ($Z=-2.524$, $p=0.012$); naming accuracy of trained items following HD-tDCS was significantly different immediately post treatment ($Z=-2.524$, $p=0.012$) and at follow up ($Z=-2.201$, $p=0.028$). Significant differences on untrained item accuracy for follow-up compared to baseline were observed ($Z=-2.127$, $p=0.033$). All pairwise comparisons for response time of accurate naming were significant (Z range -2.380 to -2.521, p range 0.012 to 0.017).

Change in accuracy of trained items was numerically higher for HD-tDCS compared to CS-tDCS for 6 of the 8 patients immediately post-treatment and for 5 of the 8 patients at follow up. This was not clearly mirrored by response time values; greater reductions in response time of accurate naming of trained items were observed for 6 of the 8 patients immediately post CS-tDCS compared to HD-tDCS, but for 5 of the 8 patients one week post HD-tDCS compared to CS-tDCS. Differences in outcome measures between the two brain stimulation conditions were not statistically significant. If future studies were to utilize accuracy of trained items as the primary outcome measure, then an efficacy study to prove the superiority of HD-tDCS over CS-tDCS (with a 5% error margin) would have a 85% chance of success if it used N = 53 subjects assuming that the relative gain

Table 2
Change in accuracy (and *Response Time of Accurate Naming*) immediately post-treatment and at 1 week follow-up

	Post-treatment > Baseline				1 Week Follow-Up > Baseline			
Patient	CS-T	HD-T	CS-UT	HD-UT	CS-T	HD-T	CS-UT	HD-UT
1	3	1	0	3	1.5	0	0	2
	−238.54	*−204.29*	*−241.76*	*−268.39*	*−216.59*	*−236.57*	*−244.85*	*−255.78*
2	2	3.5	.5	1.5	1	6	1.5	3.5
	−313.10	*−249.24*	*−365.31*	*−167.09*	*−202.87*	*−309.86*	*−164.33*	*−332.91*
3	3	4	5	−1	3	5	0	−.5
	−161.10	*−152.79*	*−74.79*	*−392.59*	*−218.40*	*−216.57*	*−258.97*	*−279.76*
4	6	9.5	−1.5	0	7	7	−.5	2.5
	−64.32	*−366.88*	*−181.17*	*−307.34*	*−194.65*	*−382.86*	*−147.43*	*−326.76*
5	3.5	11.5	0.5	1	4.5	12	2	2
	−161.28	*−90.61*	*−283.65*	*36.10*	*−148.20*	*−92.16*	*−243.12*	*27.33*
6	7.5	1.5	3	.5	6.5	2	2	−.5
	−436.16	*−353.90*	*−119.10*	*−493.51*	*−510.22*	*−310.62*	*−255.14*	*−491.32*
7	2	5	0	1.5	3.5	5.5	−.5	2
	−136.23	*−166.27*	*−66.34*	*−79.42*	*−114.83*	*−138.75*	*−96.53*	*−73.13*
8	8	9	−1.5	−.5	5.5	7.5	−2.5	−1
	−172.67	*−122.11*	*−87.41*	*−119.09*	*−144.12*	*−167.05*	*−70.79*	*−108.53*
M	4.38	5.63	0.75	0.75	4.06	5.63	0.25	1.25
	−210.43	*−213.26*	*−177.44*	*−223.92*	*−218.74*	*−231.81*	*−185.14*	*−230.11*
SD	2.43	3.91	2.22	1.28	2.21	3.61	1.54	1.67
	116.75	*102.80*	*110.27*	*174.35*	*123.71*	*98.36*	*75.65*	*167.74*

Abbreviations: CS−T, Conventional sponge-based tDCS treatment – Trained items; CS-UT, Conventional sponge-based tDCS treatment – Untrained items; HD-T, High-definition tDCS treatment – Trained items; HD-UT, High-definition tDCS treatment – Untrained items.

of HD- over CS-tDCS is 1.56 ± 3.7, as was observed in this study.

4. Discussion

We designed and automated techniques for individualized modeling and targeting. A process that previously took several days of expert time has been reduced to hours of largely automated processing, demonstrating implementation of these techniques could be possible in a clinical research setting. We also developed, built, and tested a multi-channel HD-tDCS device based on clinician feedback (Fig. 3). This device proved to be clinician-friendly and durable throughout this feasibility study during which patients received brain stimulation as an adjuvant to computerized treatment. Neither stimulation condition significantly changed discomfort ratings or measures of cardiovascular arousal, despite the larger total current intensity used for HD-tDCS. The primary outcome measures, naming accuracy and naming response time, improved with treatment for both CS- and HD-tDCS.

The study protocol was implemented in its entirety, with both conditions comparable in terms of ease of implementation, session duration, etc. Clinician competency for this study included extensive training/experience with both brain stimulation techniques as well as experience with adults with communication impairment. It could be argued that the latter competency is not necessary, since both devices are easy to operate and speech-language treatment is computerized. However, we suggest that clinical experience with this population is necessary for informed consent, adequate explanation of study tasks/procedures, accurate and reliable assessment, adequate response to questions or concerns (that may be difficult to understand and/or conveyed in alternative communication modalities), and for successful clinician-patient interaction (which guards against attrition). Intervention integrity was high – sessions were consistently delivered to each patient in the same manner (scripted instructions, prescribed amount of turns, same type of feedback, etc.). Dose integrity for the computerized treatment was ensured by the nature of the treatment delivery. However, though the same mA for each condition was administered to each patient for the same duration, it is clear that dosage, if defined by electrical field at target, was not equal for all participants (see Fig. 2). Reliability between clinicians was not assessed since one clinician administered all sessions, but given the ease of operation, reliability between clinicians for future similar studies is expected to be high. The computerized treatment, brain stimulation conditions, and study schedule were acceptable to patients and the clinician.

Changes in accuracy reported here are comparable to previous studies with this population (Baker et al., 2010; Fridriksson et al., 2011; Fiori et al., 2011). The changes in naming response time are notably different from previous research (Fridriksson et al., 2011) and can likely be attributed to the differences in population. In Fridriksson et al. (2011), patients were selected because of their fairly homogeneous lesion location and aphasia type/severity. As 7 of 8 patients were classified as anomic and thus expected to be at or near ceiling for picture naming accuracy, response time of accurate naming was selected as the variable of interest. In the current study, aphasia type and severity varied, and most patients had much room for improvement. It is likely that a speed-accuracy tradeoff can partially account for the differences in response time between the two studies, for instead of just becoming more efficient at retrieving words they could already access, the patients in this study were also working to retrieve words that they may have relearned, and often this retrieval was marked by long pauses, self-corrections, etc. This highlights the need for careful consideration of the study population when selecting dependent variables for future studies. Because of this, sample size estimates for future research were only performed for accuracy measures.

We elected to compare outcomes following application of 1 mA CS-tDCS, as in previous studies performed by our research group, to a 2 mA HD-tDCS expected to match the CS-tDCS in terms of scalp sensations (determined via modeling of current density at skin) but deliver the maximum current allowed within safety limits. Although the study showed no significant differences between the two conditions, the numerically higher values observed for HD-tDCS might not have occurred had it been a 2 mA across both conditions. However, the primary goal of this study was to determine if this new technique could be administered with comparable comfort levels, study schedules, clinician competency, etc. when compared to CS-tDCS with comparable (or better) outcomes in order to determine whether future HD-tDCS studies were warranted. Additional limitations include a small sample size and that patients were not blinded to their brain stimulation conditions. Lastly, this and other studies (e.g., Datta et al., 2009, 2012; Krause & Cohen Kadosh, 2014) reveal that the dosage (electrical field at target) likely differs dramatically among individuals due to individual lesion anatomy, despite the same mA being applied to the

scalp. Future work should focus on understanding the relationship between dosage and behavioral outcomes if dose-response relationships for these techniques are to be revealed.

Brain stimulation to enhance treatment outcomes is an exciting area of research for chronic clinical populations, since the presence of a chronic impairment means that treatment has so far offered guarded benefit. The computerized treatment administered here was selected because it has been shown to lead to improvements in naming and can be administered in a controlled manner. For these reasons, it is an ideal treatment approach to use to demonstrate the enhancing effects of tDCS in research settings with access to the resources required for such a study (e.g., neuroimaging, modeling/targeting software). This does not mean that this approach, in its current form, is practical for clinical delivery, nor do we promote it as an ideal clinical treatment approach that enhances communication abilities in PWAs. To be truly relevant for rehabilitation, we should not only determine whether or not tDCS (CS- or HD-) simply enhances outcomes (i.e., statistically and practically significant) but also investigate whether tDCS moves the patient closer to making improvements that are noticeable in their daily lives (i.e., clinically and personally significant; Holland & Crinion, 2012; Bothe & Richardson, 2011). Such investigations will move the field closer to a truly clinically useful product, for which demand is likely to be high.

To our knowledge, this is the first study to use HD-tDCS in conjunction with week-long behavioral therapy in a diverse group of post-stroke patients with mild to moderate aphasia. Technical feasibility of individualized modeling was demonstrated and a clinician-friendly HD-tDCS device was developed. Initial feasibility testing shows that HD treatment studies can be implemented when designed similarly to documented CS-tDCS studies, and is likely to be acceptable to patients and clinicians. Preliminary efficacy data suggest that HD effects are at least comparable to CS-tDCS. Therefore, we believe HD-tDCS holds promise as a clinical technique and warrants further investigation. This study documents the safety and tolerability of this treatment in a small cohort and lays the groundwork for the next phase of trials to begin.

Acknowledgments

The authors would like to thank Yu Huang for generating the volumetric models of the stroke patients and additional students from Department of Biomedical Engineering at CCNY who contributed significant time and effort to manually improve the segmentation of these MRI scans. We would also like to thank the patients and members of the Aphasia Laboratory, University of South Carolina, for their tireless efforts during this project.

Declaration of interest

This work was partially supported by NIH-NINDS grant R41 NS076123 “Targeted transcranial electrotherapy system to accelerate stroke recovery” and a CUNY-CAT matching grant supported by NYSTAR. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Drs. Datta and Parra have equity in Soterix Medical Inc., and CUNY has patents on brain stimulation with Drs. Datta, Dmochowski, and Parra as inventors.

References

Baker, J. M., Rorden, C., & Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke 41*, 1229-1236.

Bastani, A., & Jaberzadeh, S. Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: A systematic review and meta-analysis. *Clinical Neurophysiology*, *123*, 644-657.

Borckardt, J. J., Bikson, M., Frohman, H., Reeves, S. T., Datta, A., Bansal, V., & et al. (2012). A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. *Journal of Pain*, *13*, 112-120.

Bothe, A. K., & Richardson, J. D. (2011). Statistical, practical, clinical, and personal significance: Definitions and applications in speech-language pathology. *American Journal of Speech Language Pathology*, *20*, 233-242.

Bowen, D. J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D.,... Fernandez. M. (2009). How we design feasibility studies. *American Journal of Preventive Medicine*. *36*, 452-457.

Caparelli-Daquer, E. M., Zimmerman, T. J., Mooshagian, E., Parra, L. C., Rice, J. K., Datta, A., & et al. (2012). A pilot study on effects of 4×1 high-definition tDCS on motor cortex excitability. *Conference Proceedings of the IEEE Engineering in Medicine and Biology Society*, 735-738.

Cerruti, C. & Schlaug, G. (2009). Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. *Journal of Cognitive Neuroscience*, *21*, 1980-1987.

Cohen Kadosh, R., Soskic, S., Iuculano, T., Kanai, R., & Walsh, V. (2010). Modulating neuronal activity produces specific and long-lasting changes in numerical competence. *Current Biology*, *20*, 2016-2020.

Coltheart, M. (1981). The MRC psycholinguistic database. *Quarterly Journal of Experimental Psychology Section A. 33*, 497-505.

Conn, V. S., Algase, D. L., Rawl, S. M., Zerwic, J. J., & Wyman, J. F. (2010). Publishing pilot intervention work. *Western Journal of Nursing Research, 32*, 994-1010.

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., & Bikson, M. (2009). Gyri-precise head model of transcranial DC stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimulation*, *2*, 201-207.

Datta, A., Truong, D., Minhas, P., Parra, L. C., & Bikson, M. (2012). Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. *Frontiers in Psychiatry*, *3*, 91.

Datta, A., Baker, J. M., Bikson, M., & Fridriksson, J. (2011). Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. *Brain Stimulation*, *4*, 169-174.

Dmochowski, J. P., Datta, A., Bikson, M., Su, Y., & Parra, L. C. (2011). Optimized multi-electrode stimulation increases focality and intensity at target. *Journal of Neural Engineering*, *8*, 046011.

Dmochowski, J. P., Datta, A., Huang, Y., Richardson, J. D., Bikson, M., Fridriksson, J., & Parra, L. C. (2013). Targeted transcranial direct current stimulation for rehabilitation after stroke. *NeuroImage 75*, 12-19.

Dockery, C. A., Hueckel-Weng, R., Birbaumer, N., & Plewnia, C. (2009). Enhancement of planning ability by transcranial direct current stimulation. *Journal of Neuroscience*, *29*, 7271-7277.

Fiori, V., Coccia, M., Marinelli, C. V., Vecchi, V., Ceravolo, M. G., Provinciali, L.,... Marangolo, P. (2011). Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. *Journal of Cognitive Neuroscience*, *23*, 2309-2323.

Frances, W. N., & Kucera, H. (1982). *Frequency analysis of English usage*. Boston, MA: Houghton Mifflin.

Fregni, F., & Pascual-Leone, A. (2007). Technology insight: Noninvasive brain stimulation in neurology perspectives on the therapeutic potential of rTMS and tDCS. *Nature Reviews Neurology*, *3*, 383-393.

Fridriksson, J. (2010). Preservation and modulation of specific left hemisphere regions is vital for treated recovery from anomia in stroke. *Journal of Neuroscience*, *30*, 11558-11564.

Fridriksson, J., Baker, J. M., Whiteside, J., Eoute, D. Jr., Moser, D., Vesselinov, R., & Rorden, C. (2009). Treating visual speech perception to improve speech production in nonfluent aphasia. *Stroke 40*, 853-858.

Fridriksson, J., Richardson, J. D., Baker, J. M., & Rorden, C. (2011). Transcranial direct current stimulation improves naming reaction time in fluent aphasia: A double-blind sham-controlled study. *Stroke 42*, 819-821.

Fridriksson, J., Richardson, J. D., Fillmore, P., & Cai, B. (2012). Left hemisphere plasticity and aphasia recovery. *Neuroimage*, *60*, 854-863.

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: Potential implications for motor learning. *Neuron 66*, 198-204.

Harty, S., Robertson, I. H., Miniussi, C., Sheehy, O. C., Devine, C. A., McCreery, S., O'Connell, R. G. (2014). Transcranial direct current stimulation over right dorsolateral prefrontal cortex enhances error awareness in older age. *The Journal of Neuroscience*, *34*(10), 3646-3652.

Holland, R., & Crinion, J. (2012). Can tDCS enhance treatment of aphasia after stroke? *Aphasiology*, *26*, 1169-1191.

Huang, Y., Su, Y., Rorden, C., Dmochowski, J., Datta, A., & Parra, L. C. (2012). An automated method for high-definition transcranial direct current stimulation modeling. *Conference Proceedings of the IEEE Engineering in Medicine and Biology Society*, 5376-5379.

Hummel, F. C., & Cohen, L. G. (2005). Drivers of brain plasticity. *Current Opinions in Neurology*, *18*, 667-674.

Kertesz, A. (2007). *Western Aphasia Battery – Revised*. San Antonio, TX: Harcourt Assessment, Inc.

Krause, B. & Cohen Kadosh, R. (2014). Not all brains are created equal: The relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience*, *8*, 25.

Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and 4×1 high-definition tDCS: A neurophysiological study. *Brain Stimulation*, *6*, 644-648.

Lee, S. J. & Chun, M. H. (2014). Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. *Archives of Physical Medicine and Rehabilitation*, *95*(3), 431-438.

Lindenberg, R., Renga, V., Zhu, L. L., Nair, D., & Schlaug, G. (2010). Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology*, *75*, 2176-2184.

Mendonca, M. E., Santana, M. B., Baptista, A. F., Datta, A., Bikson, M., Fregni, F., & Araujo, C. P. (2011). Transcranial DC stimulation in fibromyalgia: Optimized cortical target supported by high-resolution computational models. *Joural of Pain*, *12*, 610-617.

Minhas, P., Bansal, V., Patel, J., Ho, J. S, Diaz, J., Datta, A., & Bikson, A. (2010). Electrodes for high-definition transcraneous DC stimulation for application in drug delivery and electrotherapy, including tDCS. *Journal of Neuroscience Methods*, *190*, 188-197.

Moliadze, V., Antal, A., & Paulus, W. (2010). Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic reference electrodes. *Clinical Neurophysiology*, *121*, 2165-2171.

Nitsche, M. A., Liebetanz, D., Schlitterlau, A., Henschke, U., Fricke, K., Frommann, K., & et al. (2004). GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. The *European Journal of Neuroscience*, *19*, 2720-2726.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology*, *527*, 633-639.

Patel, J., Bansal, V., Minha, P., Ho, J., Datta, A., & Bikson, M. (2009). High-density transcranial direct current stimulation (HD-tDCS): Skin safety and comfort. *Journal of Medical Devices*, *3*, 027554.

Park, J-H., Hong, S. B., Kim, D-W., Suh, M., & Im, C-H. (2011). A novel array-type transcranial direct current stimulation (tDCS) system for accurate focusing on targeted brain areas. *IEEE Transactions on Magnetics*, *47*(5), 882-885.

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*, *72*, 208-214.

Schulz, R., Gerloff, C., & Hummel, F. C. (2013). Non-invasive brain stimulation in neurological diseases. *Neuropharmacology*, **64**, 579-587.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T,& et al. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience, 29*, 5202-5206.

Yang, E. J., Baek, S. R., Shin, J., Lim, J. Y., Jang, H. J., Kim, Y. K., & Paik, N. J. (2012). Effects of transcranial direct current stimulation (tDCS) on post-stroke dysphagia. *Restorative Neurology and Neuroscience, 30*, 303-311.