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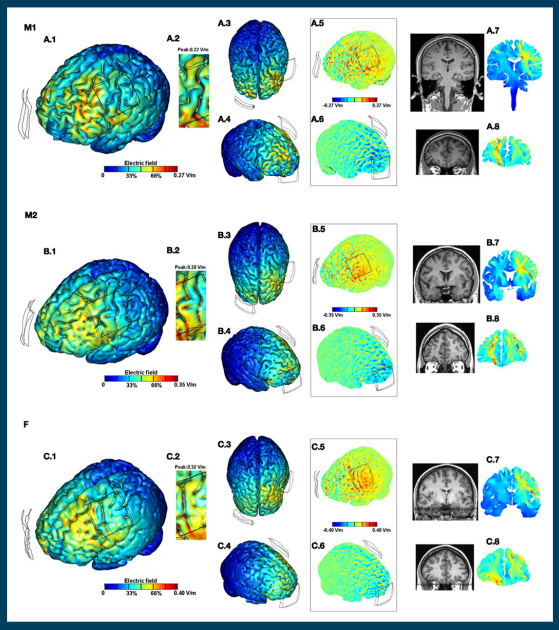

THE FRONTIERS OF CLINICAL RESEARCH ON TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) IN NEUROPSYCHIATRY

Topic Editors
Alberto Priori, Andre R. Brunoni, Felipe Fregni, Paulo S. Boggio and Roberta Ferrucci

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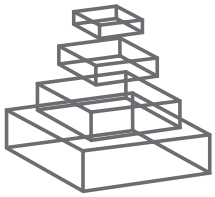

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THE FRONTIERS OF CLINICAL RESEARCH ON TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) IN NEUROPSYCHIATRY

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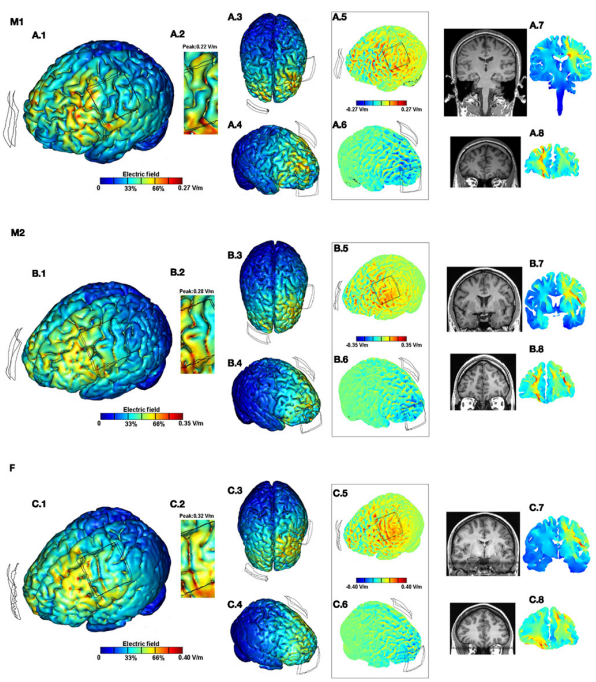

Computational models showing the current electric flow from the electrodes through the brain.

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EDITORIAL
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Transcranial direct current stimulation: challenges, opportunities, and impact on psychiatry and neurorehabilitation

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The simplicity of the technique of transcranial direct current stimulation (tDCS) can be observed as it consists of a current generator and two electrodes that are placed over the scalp and can deliver weak direct currents. Despite its simplicity, the field of non-invasive brain stimulation has had a rapid and exponential increase in the past 10 years. It is in fact an "old, new" technique – as external brain electric stimulation with electric currents has been recurrently described in medical literature since ancient times (Brunoni et al., 2011b), although the technique was reappraised only recently after the seminal studies of Priori et al. (1998) and Nitsche and Paulus (2000), which showed that it could modify cortical excitability in a polarity-dependent manner, i.e., while anode induces neuronal depolarization and thus activation of neural networks beneath the electrode, the cathode induces the opposite effects (i.e., hyperpolarization and consequent inhibition). From 1998 onward, several studies showed that tDCS modulates a plethora of behavioral, sensorial, or motor effects according to parameters of stimulation and subjects' characteristics. Two important characteristics of tDCS – the duration of its effects and its safety – have attracted the attention of a large number of scientists and clinicians. Indeed tDCS effects can last for several hours beyond the period of stimulation in some cases (Fregni and Pascual-Leone, 2007) and induce changes in brain biochemistry (Rango et al., 2008). In addition, studies in experimental animals show that tDCS is safe (Liebetanz et al., 2009), and a systematic review found that adverse effects are mild and transient (Brunoni et al., 2011a).

Another important characteristic of tDCS is that it can potentially be adapted for home-use, which would bring about an important advance to the therapeutic field of brain stimulation (Priori et al., 2009). From a methodological perspective, it has a reliable sham method as compared with, for instance, rTMS. Such characteristics (ease of use, low cost, portability, safe, potent effects) render tDCS a sound device for further clinical research, either as a substitutive therapy or a complementary treatment for other interventions (drug therapy, physical therapy, psychotherapy, and so forth) (Brunoni et al., 2011c), especially considering patients that are unable or unwilling to receive standard treatments.

Nonetheless, tDCS clinical trials are still in their infancy. One possible reason is that tDCS use requires basic knowledge on a neural basis of electrical current fields and neuroscience. In fact, an incorrect electrode montage or stimulation of the "wrong" area might generate non-specific or even negative effects (Datta et al., 2010; Mahmoudi et al., 2010; Mendonca et al., 2011). Therefore, it is more difficult to observe positive clinical effects by serendipity – also because tDCS has presently no standard clinical use, all effects can only be observed through research. Further, tDCS trials are methodologically complicated due to attrition, since the protocols demand daily stimulation for 1–4 weeks. A possible solution would be to use portable devices – specific tailored caps could be assembled in for targeting only the desired scalp areas. Furthermore, tDCS may be a device with little commercial interest compared to other medicines or even rTMS – in fact, by being *too* affordable and with a limited possibility of patenting, more robust business ventures are easily discouraged to develop tDCS commercially. Not surprisingly, at the present time tDCS research is mainly conducted in academic settings, usually with public grants. Nevertheless, this scenario could rapidly change depending on whether effective parameters of stimulation and findings are shown in clinical research. Finally, a simple reason to explain the current stage of development of tDCS is timing. Clinical trials, as well as the reporting and dissemination of results, usually has a significant time span.

Considering such challenges, we proposed a Research Topic in *Frontiers in Psychiatry*, named *The frontiers of clinical research on tDCS in neuropsychiatry*. The results were surprisingly positive, with 22 articles from new and experienced research groups that, considered together, represent a robust contribution to the advancement of the field. We are also grateful to all the reviewers – many of them productive researchers in the field – for their invaluable help in making suggestions that ultimately improved the manuscripts significantly. The articles hereby presented are divided in five main sections – in the first one, the neurobiological effects of tDCS are reviewed (Medeiros et al., 2012) and original articles on the electrophysiological effects of tDCS on visuo-spatial working memory (Heimrath et al., 2012), human color discrimination (Costa et al., 2012), and motor cortical excitability (Chaieb et al., 2012) are

presented. The second section contains original articles exploring the behavioral effects of tDCS such as on the saccade task (Kanai et al., 2012), automatic verbal processes (Vannorsdall et al., 2012), working memory (Jones and Berryhill, 2012), emotional processing (Nitsche et al., 2012) and production of untruthful responses (Fecteau et al., 2012), and one review by Brasil-Neto (2012) on tDCS' effects in learning and memory. The third section shows original articles on the clinical effects of tDCS on tinnitus (De Ridder and Vanneste, 2012), major depressive disorder (Blumberger et al., 2012; Knotkova et al., 2012) and pain (DosSantos et al., 2012), and reviews its effects on Alzheimer's disease (Hansen, 2012), stroke (Adeyemo et al., 2012; Madhavan and Shah, 2012), and smoking addiction (Fraser and Rosen, 2012). The fourth section presents computational theoretical models of tDCS for further application in clinical practice (Datta et al., 2012; Neuling et al., 2012; Sadleir et al., 2012). The last section reviews the application of spinal tDCS (Cogiamanian et al., 2012).

Moving tDCS research from bench to bedside has significant challenges. Nevertheless, there are opportunities for tDCS development as pharmacotherapy is reaching an efficacy and safety plateau and there are still unmet demands for the treatment of several disorders. tDCS therefore represents an interesting alternative that can offer additional therapeutic gains with a minimum of or no side effects. Whether the obstacles of clinical trials are solved or not, this collection of articles presented in this Research Topic provides promising evidence that tDCS could rise in the near future as a novel therapeutic tool and have a significant impact n psychiatry and neurorehabilitation.

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ORIGINAL RESEARCH ARTICLE
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Transcranial direct current stimulation modulates human color discrimination in a pathway-specific manner

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Previous research showed that transcranial direct current stimulation (tDCS) can modulate visual cortex excitability. However, there is no experiment on the effects of tDCS on color perception to date. The present study aimed to investigate the effects of tDCS on color discrimination tasks. Fifteen healthy subjects (mean age of 25.6 ± 4.4 years) were tested with Cambridge Color Test 2.0 (Trivector and ellipses protocols) and a Forced-choice Spatial Color Contrast Sensitivity task (vertical red-green sinusoidal grating) while receiving tDCS. Anodal, cathodal, and sham tDCS were delivered at Oz for 22 min using two square electrodes (25 cm^2 with a current of 1.5 mA) in sessions separated by 7 days. Anodal tDCS significantly increased tritan sensitivity ($p < 0.01$) and had no significant effect on protan, deutan, or red-green grating discrimination. The effects on the tritan discrimination returned to baseline after 15 min ($p < 0.01$). Cathodal tDCS reduced the sensitivity in the deutan axis and increased sensitivity in the tritan axis ($p < 0.05$). The lack of anodal tDCS effects in the protan, deutan, and red-green grating sensitivities could be explained by a "ceiling effect" since adults in this age range tend to have optimal color discrimination performance for these hues. The differential effects of cathodal tDCS on tritan and deutan sensitivities and the absence of the proposed ceiling effects for the tritan axes might be explained by Parvocellular (P) and Koniocellular (K) systems with regard to their functional, physiological, and anatomical differences. The results also support the existence of a systematic segregation of P and K color-coding cells in V1. Future research and possible clinical implications are discussed.

Keywords: color vision, koniocellular pathway, parvocellular pathway, V1, tDCS, transcranial direct current stimulation

INTRODUCTION

Color vision is a popular model system for information processing in neural circuits and human color perception has been successfully used as a model to assess the functional status of the central nervous system (Gobba and Cavalleri, 2003; Ventura et al., 2003, 2004, 2005, 2007; Silva et al., 2005; Costa et al., 2006, 2007; Feitosa-Santana et al., 2008, 2010; Moura et al., 2008; Barboni et al., 2009; Conway et al., 2010). Current understanding of the human color perception system can be considered extensive when compared to our understanding of other sensory systems. On the other hand several relevant unanswered questions remain, especially concerning the organization and tuning of color-coding cells in V1 and the organization of color processing pathways in the extrastriate visual cortex. The variety of congenital and acquired color vision defects and the lack of effective rehabilitative procedures are also noteworthy. As pointed by Simunovic (2010), the current management of congenital color vision deficiency is mostly limited to career counseling although animal experiments point to a future for gene therapy (Mancuso et al., 2009).

To date, the possibility of modulating human color vision using transcranial non-invasive neuromodulatory techniques was not yet evaluated. Techniques such as transcranial direct current stimulation (tDCS) can complement current research by introducing a causal approach in which the effects of inhibitory and excitatory interventions over a specific brain area can be evaluated in a specific task. Several lines of research in neuroscience benefited from using this rationale (for reviews see Nitsche et al., 2008; Zaghi et al., 2010).

Transcranial direct current stimulation is a non-invasive brain modulation technique that uses weak direct currents with polarity-dependent functional effects: cathodal currents being generally inhibitory while anodal being excitatory (Nitsche and Paulus, 2000; Nitsche et al., 2008). In the past 10 years researchers were successful in using tDCS to modulate human visual system performance (Antal and Paulus, 2008). Significant results include improvements in luminance contrast sensitivity (Antal et al., 2001, 2004a; Accornero et al., 2007), phosphene threshold reduction (Antal et al., 2003a,b), sensitivity in central visual field measured by standard automated perimetry (Kraft et al., 2010), and different visuomotor skills (Antal et al., 2004b,c; Bolognini et al., 2010a,b). In addition, tDCS has modulatory effects on multisensory integration tasks (Bolognini et al., 2010a, 2011) and illusory phenomena (Varga et al., 2007; Bolognini et al., 2011).

The use of tDCS as a tool for stroke patient's rehabilitation is promising since these patients show improvements in visual system performance even after one single tDCS session (Ko et al., 2008; Halko et al., 2011). Similarly in congenital and acquired color vision deficiencies tDCS might be used to improve the remaining color discrimination performance. Furthermore, gene therapy is quickly advancing as a potential treatment for congenital color deficiency, but if applied in humans it will probably be accompanied by behavioral training (Mancuso et al., 2009). In this panorama tDCS could be a valuable tool to boost the behavioral outcomes of the treatments.

If tDCS can affect color perception, future research applying tDCS to the visual cortex during visual discrimination tasks should take into account the color parameters of the stimuli used. When taken together, the abovementioned arguments justify the urgent and crucial nature of the current investigation. In the present study we examined the effect of tDCS on color discrimination thresholds and chromatic contrast thresholds using current psychophysical methodology. Considering the literature on tDCS modulation of visual perception, we hypothesize that tDCS will have a significant effect on color discrimination.

MATERIALS AND METHODS

PARTICIPANTS AND STUDY DESIGN

We conducted a randomized, single-blind repeated-measures study to evaluate the effects of tDCS delivered to the visual cortex on color discrimination thresholds and on chromatic contrast thresholds. Fifteen healthy subjects (mean age of 25.6 ± 4.4 years) with no history of neuropsychiatric or visual system disorders participated in this study. Subjects had no metallic implants and were not under treatment with medication that could affect central nervous system function and were not smokers or users of psychoactive drugs. All participants had normal or corrected to normal visual acuity (Snellen 20/20).

Participants were submitted to three sessions of tDCS: one for sham stimulation, one for anodal, and one for cathodal stimulation of the visual cortex. The sessions were separated by an interval of 7 days, and all procedures were the same in the three sessions, except for the tDCS modality. The order of the sessions and the order of the visual tests applied in each session were randomized across subjects and across sessions. The sessions for each participant occurred at a similar time of the day to try to avoid eventual confounding factors. The participants received 5 min of tDCS only, followed by 17 min of tDCS during the visual tests, totalizing 22 min of stimulation. Fifteen minutes after the end of the stimulation the participants were tested again with the Cambridge Color Test (CCT) Trivector protocol (see Color Vision Assessment). A summary of the session *procedures* is presented in **Figure 1**.

The study was approved by the institutional ethics committees of the University of São Paulo Biomedical Sciences Institute (1025/CEP) and Mackenzie Presbyterian University, Brazil, and registered at the National Ethics Committee (SISNEP, Brazil – CAAE – 0097.0.272.134-11). Written informed consent was obtained from all participants.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Transcranial direct current stimulation was delivered through two square (25 cm^2) saline-soaked sponge electrodes connected to a specially developed, battery-driven direct current stimulator with a maximum output of 2 mA. Stimulation intensity was set at 1.5 mA, generating a current density of 0.06 mA/cm^2. Electrodes were placed at Oz and Cz (according to the International 10-20 EEG System, Jasper, 1958). For anodal stimulation, anode electrode was placed over Oz and the cathode over Cz, while the contrary was true for the cathodal tDCS condition. Non-conductive elastic bandages were used to hold the electrodes in place.

In each session the current was ramped from 0 to 1.5 mA in 10 s. In the sham stimulation condition the current was ramped down after 30 s of stimulation, the equipment's sham mode was activated and the session was conducted in the same way as the active stimulation sessions. In sham mode the equipment continues working without passing current through the electrodes and all stimulation parameters are visible in the display, resembling an active stimulation condition. By receiving 30 s of stimulation the participant can feel the initial skin sensation associated with active tDCS but the stimulation is considered ineffectual for neuromodulation purposes. This procedure is considered efficient for blinding subjects with respect to stimulation parameters (Gandiga et al., 2006).

COLOR VISION ASSESSMENT

Color vision was assessed with two computer based psychophysical tests: Cambridge Color Test 2.0 (Cambridge Research Systems) and a Forced-choice Spatial Chromatic Contrast Sensitivity task (CCS) developed by our group. Both tests ran on a Dell microcomputer and the stimuli were presented through a VSG 2/5 Visual Stimulus Generator in a Viewsonic G90fB 19″ CRT monitor. The monitor's gamma correction was done immediately before the beginning of the research using an Optical 200E Photometer (Cambridge Research Systems). Both tests were performed binocularly in a dark room with the participants seated 3 m away from the monitor screen and using a remote control (CT6 model, Cambridge Research Systems).

The CCT is a color discrimination test that uses pseudoisochromatic stimuli in a luminance and spatial noise background (**Figure 2A**), with stimulus parameters that are optimal for color vision assessment (Mollon and Reffin, 1989; Reffin et al., 1991; Regan et al., 1994; Ventura et al., 2003; Costa et al., 2006). In luminance and spatial noise environment, only the chromatic characteristics of the stimulus change from trial to trial, and therefore, no confounding factors like luminance or contour cues can influence the performance. The stimuli consist of a mosaic of circles of different diameters and luminances forming the background with a subset of circles of a different chromaticity forming a target. The target is a modified Landolt "C" with 1.25° gap for a viewing distance of 2.6 m. Only two parameters vary during the test: (i) the "C" gap appears randomly oriented up, down, left, or right in each trial and (ii) the chromaticity of the target varies along pre-specified vectors in the CIE 1976 $u'v'$ color space (**Figures 2B,C**). Participants are instructed to identify the orientation of the gap in the stimulus by pressing a remote control. A four-alternative forced-choice staircase was used, where for

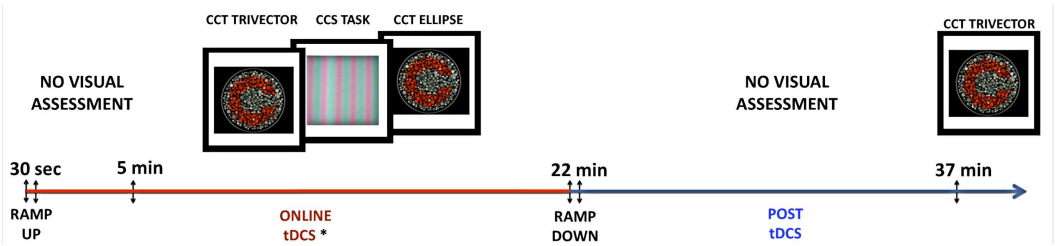

FIGURE 1 | Summary of experimental procedures. tDCS current was ramped up during the first 30 s of the procedure. Participants received 5 min of tDCS before starting the visual assessment. In each session, visual tests were performed in a random order. After 22 min of stimulation, the current would be ramped down and the participant would have a 15-min break without performing visual tests. After the break, the tDCS Trivector test was repeated without tDCS.

each correct response the chromaticity of the stimulus approached the chromaticity of the background/neutral point ($u'v'$: 0.1977; 0.4689) and for each incorrect response it moved away. For each CIE color space vector tested a threshold is calculated by averaging the values of six response reversals (by response reversals we mean one incorrect after one correct response or one correct after one incorrect response). The values averaged are the chromaticity values at the time of the response reversal). The task was terminated after a threshold was calculated for each of the color space vectors tested.

In the CCT, we used two complementary testing protocols that differed in overall duration and chromatic characteristics of the stimuli presented. The Trivector protocol estimates discrimination thresholds for the protan, deutan, and tritan color confusion vectors of the CIE 1976 $u'v'$ color space (**Figure 2B**). The three vectors are tested in random alternation in the same testing session. These confusion lines represent chromaticity values in the color space where subjects with congenital color vision defects are not able to discriminate (Pokorny et al., 1979). Protan stands for reddish, deutan for greenish, and tritan for bluish areas of the color space, stimuli preferentially processed by the L, M, and S wavelength-sensitive cone systems, respectively.

While the Trivector protocol measures thresholds for three vectors in the color space, the ellipses protocol measures thresholds for eight or more vectors around a fixed chromaticity background in the CIE 1976 $u'v'$ color space and represent an indicative of the visual system sensitivity to a broad range of hues. The eight vectors are tested two at a time, in random alternation. The vectors here are not the same as in the Trivector test. The eight vectors are separated by 45° so that we can evaluate color discrimination in directions within 360° of the CIE 1976 $u'v'$ color space. After the end of the test an ellipse is fitted onto the threshold points in the color space (**Figure 2C**). The area of that ellipse is considered an indicative of overall color discrimination. Smaller areas mean better discrimination. Another relevant ellipse parameter is the ratio between major and minor axes. A ratio of 1 indicates homogeneous discrimination around the background chromaticity, while a large ratio indicates poor discrimination along a direction in CIE space.

Finally, a Forced-choice Spatial Chromatic CCS was employed to estimate the Red-Green contrast sensitivity for a vertical sine-wave grating of three cycles per degree (**Figure 2D**, red: $u' = 0.288$, $v' = 0.480$; green: $u' = 0.150$, $v' = 0.480$). Before starting the CCS task, all subjects underwent a heterochromatic flicker photometry (20 Hz) adjustment to equate perceptually the luminance of the red and green stimuli, thus insuring that individual differences in L and M cone ratio would not influence the results through luminance cues (Mullen, 1985). In the CCS task, the grating started with a contrast value of 4% and chromaticity values according to each subject's heterochromatic flicker photometry results. We used a two-interval forced-choice psychophysical procedure. Subject's task was to discriminate the grating from the background chromaticity responding in a remote control if the grating appeared first or second in each trial. A 3×1 staircase was used, meaning that the contrast value would decrease 20% after every three consecutive correct responses and increase by 25% for each incorrect response. The test is terminated after six response reversals are obtained and a threshold is calculated by averaging the chromaticity values at the time of the response reversals.

The methods used in this color vision assessment are particularly adequate for a repeated-measures study. Systematic research has shown that learning effects do not affect CCT results after repeated examinations (Costa et al., 2006).

DATA ANALYSES

Analyses of the CCT Trivector Results employed three repeated-measures ANOVA with two within subjects factors: tDCS Stimulation (anodal, cathodal, sham) and Time (During tDCS, 15 min after tDCS). Analyses of the other tests results were performed by separate repeated-measures ANOVA with one within subjects factor (tDCS stimulation). When appropriate, the *post hoc* comparisons were carried using the Fisher LSD test. We measured the effect size using Partial Eta Squared (η_p^2) for every ANOVA.

RESULTS

The participants reported no adverse effects during or after the stimulation sessions. The ANOVA showed no effects of tDCS on the CCS thresholds [$F(2, 28) = 1.04$, $p = 0.36$, $\eta_p^2 = 0.08$]. This result suggests that only 8% of the variation in threshold values can be attributed to tDCS. The average CCS thresholds were 1.01 (±0.35), 1.05 (±0.33), and 1.13 (±0.32) percent contrast for anodal, cathodal, and sham tDCS, respectively (**Figure 3A**).

The Analyses of Variance showed no significant effect of tDCS on the average area of the CCT ellipses [$F(2, 28) = 1.15$, $p = 0.32$,

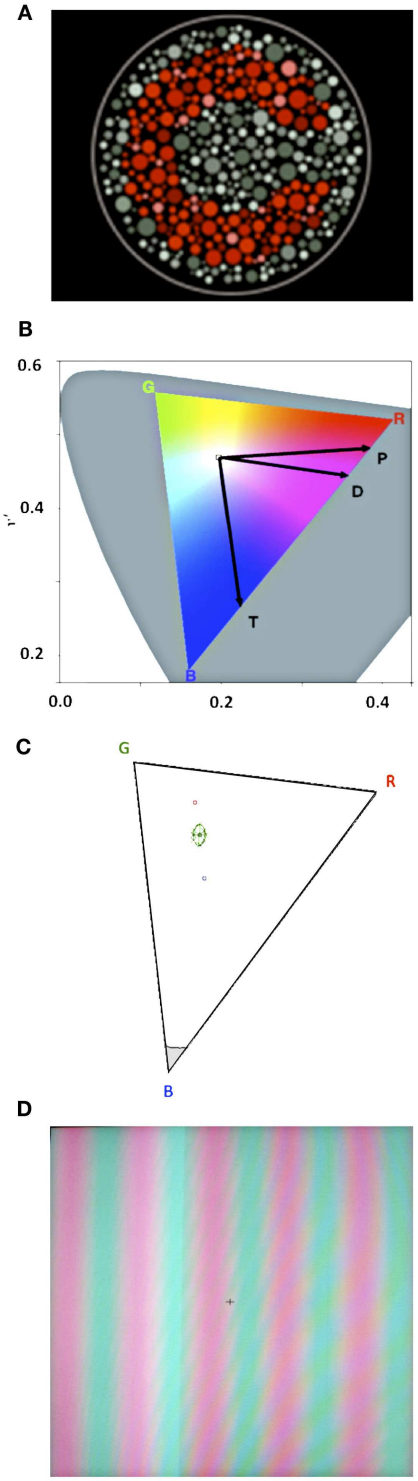

FIGURE 2 | (A) Example of the pseudoisochromatic adaptation of Landolt's C used in the Cambridge Color Test 2.0. **(B)** CIE 1976 color space with color confusion axes. "P" stands for protan, "D" stands for deutan, and "T" stands for tritan. The color triangle represents the monitor's color gamut within the CIE 1976 color space. **(C)** Example of a McAdam ellipse with eight vectors in the color triangle. **(D)** Example of a red-green s ine-wave grating.

$\eta_p^2 = 0.07$] or the ellipses axis ratio [$F(2, 28) = 1.43$, $p = 0.25$, $\eta_p^2 = 0.09$]. The area of the ellipse was on average 186.68 (±35.72), 175.92 (±26.88), and 189.27 (±36.50) $u'v'^*10^4$ vector length units for anodal, cathodal, and sham tDCS, respectively (**Figure 3B**). Average ellipse axis ratios were 1.48 (±0.23), 1.41 (±0.27), and 1.54 (±0.32) for anodal, cathodal, and sham tDCS, respectively (**Figure 3C**).

For the protan thresholds, the ANOVA showed no significant effect of tDCS [$F(2, 28) = 0.66$, $p = 0.52$, $\eta_p^2 = 0.04$] or interaction between tDCS and Time [$F(2, 28) = 0.73$, $p = 0.48$, $\eta_p^2 = 0.04$]. Average thresholds measured in $u'v'^*10^4$ vector length units for the protan axis were 28.20 (±4.54), 28.80 (±3.43), 26.87 (±4.64) $u'v'^*10^4$ for anodal, cathodal, and sham tDCS, respectively (**Figure 4A**).

For the deutan thresholds, the ANOVA showed no significant effect of tDCS [$F(2, 28) = 1.12$, $p = 0.33$, $\eta_p^2 = 0.07$] and a significant interaction between tDCS and Time [$F(2, 28) = 5.13$, $p = 0.01$, $\eta_p^2 = 0.26$]. When comparing the During tDCS results, Fisher LSD showed significant differences in cathodal vs. sham ($p = 0.02$) and cathodal vs. anodal ($p = 0.03$) comparisons, results that suggest cathodal tDCS impairs deutan discrimination (see **Figure 4B**; **Table 1**). No significant differences were found when comparing anodal vs. sham deutan thresholds ($p = 0.44$, **Figure 4B**). Cathodal vs. post cathodal deutan scores where significantly different ($p < 0.001$), suggesting a return to baseline after 15 min of the end of stimulation (**Figure 4B**). For the deutan thresholds the averages were 27.47 (±4.69), 31.60(±5.28), and 27.87 (±4.31) $u'v'^*10^4$ for anodal, cathodal, and sham tDCS, respectively.

For the tritan thresholds, the ANOVA showed a significant effect of tDCS [$F(2, 28) = 5.76$, $p < 0.01$, $\eta_p^2 = 0.29$] and interaction between tDCS and Time [$F(2,28) = 7.93$, $p < 0.01$, $\eta_p^2 = 0.36$]. *Post hoc* comparisons (**Figure 4C**; **Table 1**) showed significant differences in anodal vs. sham ($p < 0.001$), anodal vs. cathodal ($p < 0.01$), cathodal vs. sham ($p = 0.04$), and anodal vs. post anodal ($p < 0.001$). Cathodal vs. post cathodal ($p = 0.64$), post cathodal vs. sham ($p = 0.11$), and post cathodal vs. post sham (0.85) were not significantly different. Thresholds in the tritan axis were on average 32.33 (±10.75), 39.33 (±10.61), and 46.20 (±13.92) $u'v'^*10^4$ for anodal, cathodal, and sham tDCS, respectively. The results suggest a reversible improvement in tritan discrimination by tDCS as the thresholds tended to return to baseline after 15 min of the end of stimulation (**Figure 4C**).

DISCUSSION

In order to properly discuss our results, a brief review of the organization of visual processing in separate retino-cortical pathways is needed. Human color vision is trichromatic and arises from a comparison of the activation of short (S), middle (M), and long (L) wavelength-sensitive cones: cells with peak sensitivities tuned to light in the "bluish," "greenish," and "reddish" portions of the visible spectrum, respectively. Signals from the retinal ganglion cells that compare L and M cone signals project to the Parvocellular (P) retino-cortical visual pathway, while ganglion cells that compare S with combinations of L and M cone signals project to the Koniocellular (K) retino-cortical visual pathway. The P and K pathways are

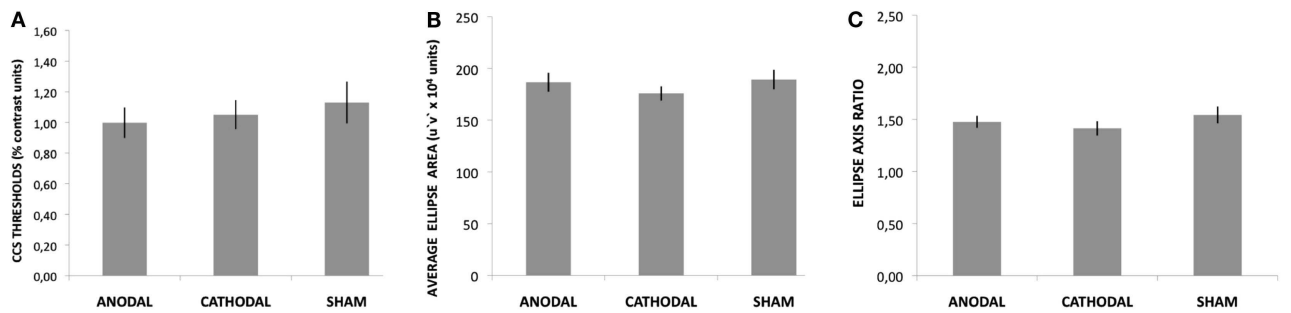

FIGURE 3 | Results for the CCS task and CCT ellipses test. None of these comparisons reached the statistical significance criteria established (95%). The bars represent the means and the vertical lines represent SE. **(A)** Average red-green thresholds measured with the CCS task. **(B)** Average ellipse area measured with the CCT ellipses test. **(C)** Average ellipse axis ratio measured with the CCT ellipses test.

Table 1 | Significance values for comparisons of deutan and tritan thresholds.

	Anodal	Cathodal	Sham	Post anodal	Post cathodal	Post sham
DEUTAN						
Anodal	–	0.003	0.444	0.523	0.609	0.732
Cathodal	0.003	–	0.022	0.016	<0.001	0.008
Sham	0.444	0.022	–	0.898	0.206	0.669
Post anodal	0.523	0.016	0.898	–	0.254	0.765
Post cathodal	0.609	<0.001	0.206	0.254	–	0.396
Post sham	0.732	0.008	0.669	0.765	0.396	–
TRITAN						
Anodal	–	0.004	≪0.001	<0.001	0.001	<0.001
Cathodal	0.004	–	0.045	0.338	0.644	0.521
Sham	≪0.001	0.045	–	0.273	0.115	0.260
Post anodal	<0.001	0.338	0.273	–	0.615	0.747
Post cathodal	0.001	0.644	0.115	0.615	–	0.856
Post sham	<0.001	0.521	0.260	0.747	0.856	–

functionally, anatomically, and phylogenetically distinct. Knowledge of primates' P and K pathways projections from the thalamus lateral geniculate nucleus (LGN) to V1 is robust: P pathway color signals target mostly the 4Cβ (with projections going to layers 4A and 6) while K signals target upper layers 1, 2, 3, and 4A. Although the laminar organization of V1 is well described, state-of-the-art methods have failed to provide a controversy-free picture of the organization of color-coding cells in V1 and some hypothesize that V1 combines part of LGN P and K inputs in arbitrary ways (Conway et al., 2010). Some authors even suggest that interlayer feedbacks and other connectivity peculiarities of V1 completely blur the P and K pathway distinction (see Sincich and Horton, 2005). For reviews on the organization of retino-cortical visual pathways see Callaway (1998, 2005), Hendry and Reid (2000), Xu et al. (2001), Gegenfurtner and Kiper (2003), Briggs and Ursey (2009), and Conway et al. (2010).

The main findings of this study were: (i) anodal tDCS was effective in improving discrimination to the blue (tritan) but did not affect the red-green (protan–deutan) discrimination measured by the CCT and red-green chromatic sensitivity measured by the CCS; (ii) cathodal tDCS had opposite effect on the tritan and deutan thresholds, increasing the sensitivity of the former and decreasing the sensitivity of the latter; (iii) both cathodal and anodal tDCS improved blue discrimination. The main discussion topics will be: (i) possible existence of a ceiling effect limiting the effectiveness of anodal tDCS on the red-green discrimination; (ii) results suggest a functional segregation of P and K pathways in V1.

Converging evidence suggested that this tDCS protocol would be effective to modulate color discrimination. First, as reviewed by Shapley and Hawken (2011), research in the last 25 years shows that V1 plays a critical role in color processing and that it is a much more relevant color-coding center than hypothesized in classic works that discussed modular organization of visual processing. Also, combining the existence of V1 cells that code color and are modulated by luminance signals (Horwitz et al., 2005), the superimposition of color and form processing in the cortex (Johnson et al., 2001; Sincich and Horton, 2005), and the existence of significant effects of tDCS on visual function when using the Oz–Cz montage (Antal et al., 2004a,b,c; Lang et al., 2007; Kraft et al., 2010) suggest that our results are not unexpected.

By using the Oz–Cz electrode montage we intended to particularly modulate the primary visual cortex's excitability, since it is a superficial cortical area expected to be under Oz electrodes. Placing the return electrode over Cz is particularly adequate for studies of the visual function, since Cz is traditionally used as reference electrode in Visual Evoked Potential studies (i.e., Norcia et al., 1989; Gawne et al., 2011) and pulses of Transcranial Magnetic Stimulation (TMS) over Cz produced no significant BOLD activity in visual areas from V1 to V4 in a concurrent TMS/fMRI study (Ruff et al., 2006). Also, there is substantial evidence that psychophysical response for simple stimuli at threshold levels may closely map the response characteristics of the different visual pathways originated in the retina (Lee, 2011). The abovementioned facts reinforce the adequacy of the methods and rationale employed here to investigate Parvo and Koniocellular pathways cortical organization.

The effect of anodal tDCS on color discrimination in the tritan axis was substantial. Sixty percent of the participants (9/15) had thresholds below 30×10^4 chromaticity difference units (in $u'v'$ color space) when receiving anodal tDCS. During the Sham tDCS condition only one participant (1/15 or 6.6%) had tritan threshold

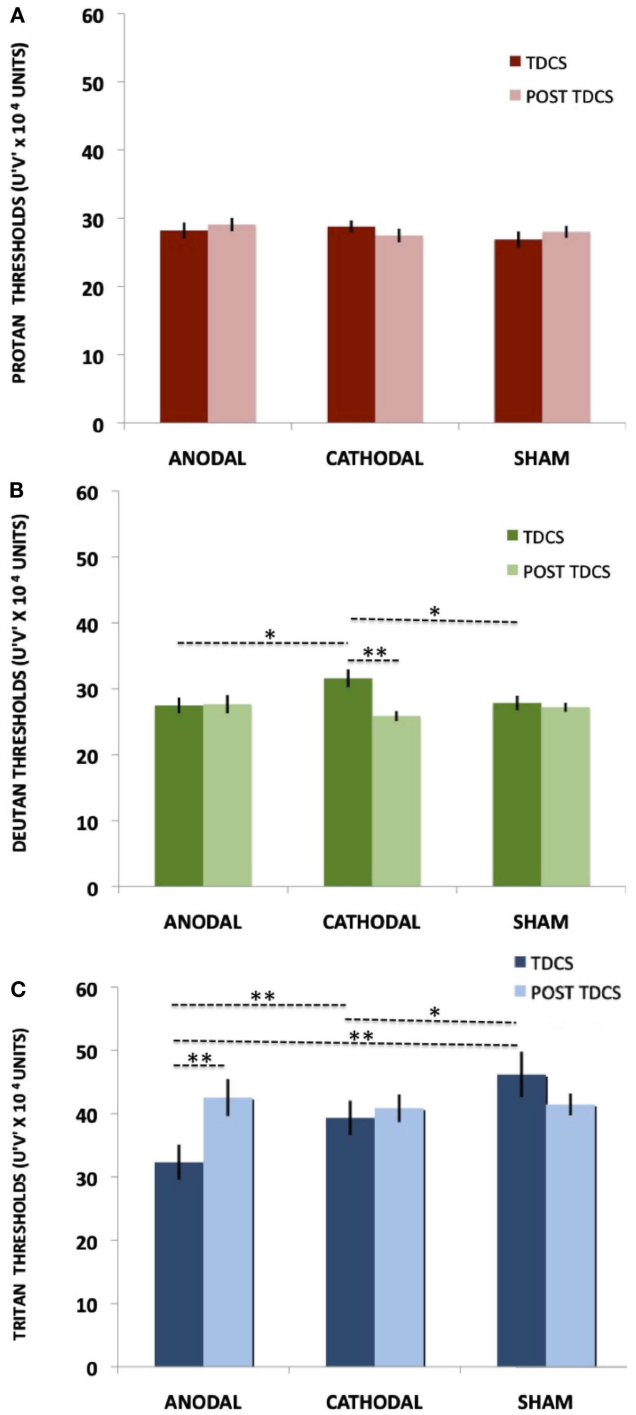

FIGURE 4 | Online tDCS and Post tDCS comparisons. The bars represent the means and the vertical lines represent SE. Statistically significant comparisons are marked with asterisks ($^{*}p < 0.05$ and $^{**}p < 0.01$). **(A)** Protan threshold values for both tDCS and post tDCS conditions. **(B)** Deutan threshold values for both tDCS and post tDCS conditions. **(C)** Tritan threshold values for both tDCS and post tDCS conditions.

values below 30×10^4 units. Costa et al. (2006) tested 36 healthy controls using the same CCT parameters and procedures, but with no tDCS. All participants had tritan discrimination thresholds higher than 30×10^4 units when performing the test binocularly. This shows that anodal tDCS decreased the tritan thresholds to levels that are below normative values. It is noteworthy that anodal tDCS was ineffective on red-green CCS or protan and deutan thresholds, that can also be considered indicatives of the red-green visual discrimination. One possible explanation for that is that koniocellular inputs from the LGN to V1 are more superficial than the parvocellular inputs. We will call this the Layer Hypothesis. On the other hand, the presence of a significant cathodal effect on deutan thresholds speaks against the layer hypothesis since there is apparently no reason why cathodal tDCS would reach layers that the anodal tDCS would not.

The fact that color discrimination is optimal in our subject's age range can be a determinant of the ineffectiveness of anodal tDCS on red-green discrimination. Previous experiments using tDCS during psychophysical and electrophysiological achromatic contrast sensitivity tests in healthy young adults suggested that ceiling effects could limit the excitatory outcome of the stimulation (Antal et al., 2001, 2004a; Antal and Paulus, 2008). It is also noteworthy that the S cone dominated K pathway is generally more fragile than the P pathway and that acquired color vision defects frequently affect the blue-yellow discrimination more intensely, fact that can be attributed to both structural and functional differences (Pokorny et al., 1979; Gobba and Cavalleri, 2003). Also, thresholds in the protan and deutan axes are generally significantly lower than in the tritan axis (Costa et al., 2006, 2007; Feitosa-Santana et al., 2010). This could also be a determinant of the existence of an anodal tDCS effect on tritan thresholds alone.

The elucidation of the mechanisms behind this proposed ceiling effect remains beyond the scope of the present work. In spite of that, we can say that the existence of a ceiling effect limiting anodal tDCS effectiveness on red-green discrimination is possible. The layer hypothesis cannot be satisfactorily invoked to explain these effects and, as we will discuss in the following paragraphs, it is unclear if there are P and K systems biophysical and morphological differences that could be determinants of this effect. Combining the abovementioned hypotheses with the fact that there is substantial data in the literature showing that a ceiling effect can limit tDCS effectiveness on the visual system (Antal et al., 2001, 2003b, 2004a; Antal and Paulus, 2008) suggest that this can be a real phenomenon relevant to our results and that further research is needed to elucidate the mechanisms behind such effect.

The existence of a qualitatively distinct effect of cathodal tDCS on tritan and deutan thresholds raises more sophisticated hypotheses. Cathodal tDCS is generally expected to impair the performance mediated by the stimulated area (as it did for the deutan discrimination), but in some circumstances, especially when involving discrimination of targets in noisy environments, cathodal tDCS can enhance performance (Antal et al., 2004c). Antal and Paulus (2008) hypothesize that cathodal tDCS can have a distinct effect on the detection of noise and target. Cathodal tDCS would diminish the overall activation level, having a stronger effect on the diffusely responding noise processing cells and therefore increasing signal-to-noise ratio and improving the performance. Although this is a plausible explanation of a

performance improvement by cathodal tDCS, it does not account for the opposite effects on tritan and deutan discriminations. This issue is not straightforward and a series of anatomical and biophysical aspects that are yet to be explored can be determinants of this phenomenon. The present work adds relevant information to this debate by showing a rare example of an increase in performance by both anodal and cathodal tDCS in the same task.

The existence of a qualitative difference of cathodal tDCS effects on tritan and deutan discrimination speaks against the Layer Hypothesis. tDCS is optimal for stimulation of superficial brain areas because the maximal current strength is achieved under the electrodes and decreases rapidly at a distance from it (Miranda et al., 2006; Wagner et al., 2007). If cell groups differ only in layer depth, tDCS effects would be only quantitatively different. If the cathodal stimulation reaches the deutan processing cells, anodal stimulation probably reaches these cells too. Therefore, the Layer Hypothesis could help to explain the absence of anodal tDCS effects on red-green discrimination, but not the opposite effects of cathodal tDCS. In order to properly discuss this series of contrasting effects we will have to consider functional, biophysical, and connectivity differences of P and K color-coding cells in V1.

While LGN P and K cells act in a fairly linear way when combining cone inputs, many color-coding V1 neurons act in non-linear ways, and some cone-opponent V1 cells are even influenced by luminance inputs (Hanazawa et al., 2000; Wachtler et al., 2003; Horwitz et al., 2005). De Valois et al. (2000) suggested that approximately half of V1 cells present significant non-linearity in their chromatic responsivity. P and K pathways are not only functionally and anatomically different but they differ in phylogenesis too, with the K pathway being significantly more ancient (Lee, 2011). Considering the functional, anatomical, and phylogenetic differences of P and K pathways, it is possible that morphological and biophysical differences exist and that this could affect tDCS effects. In fact there are morphological and biophysical differences between P and K pathway cells in photoreceptor, bipolar, and ganglion cell layers of the retina, not to mention the LGN. There are also morphological differences between part of the cells that receive P and M (Magnocellular) inputs in V1 (Sincich and Horton, 2005) and in principle different cell types could be distinctively affected by tDCS.

Apart from these, the existence of biophysical and the extent of morphological differences between primate V1 cells receiving P and K inputs is still unclear (Hendry and Reid, 2000; Shostak et al., 2002; Casagrande et al., 2007) and it is still to be discovered if differences at these levels could help to explain the differential effect of cathodal tDCS on deutan and tritan discriminations. Actually, according to Shostak et al. (2002), the morphologic differences between P and K projections from the LGN to V1 seem to be limited to axonal terminal sizes and most of the differences seem to be connectional. These morphologic differences could not fully explain the differential effects of cathodal tDCS. It is likely that P and K inputs in V1 differ mostly in connectivity, since there are several relevant steps of sensory codification between the photoreceptors and V1 and differences at the biophysical level are more likely to be found at the level of the retina or LGN (Shostak et al., 2002; Sincich and Horton, 2005).

It is clear that tDCS is not focal or specific enough to allow definitive conclusions about the nature of the behavioral modulation reported here. Morphological, connectional, or biophysical differences between P and K cells cannot be satisfactorily invoked to account for our results. Notwithstanding, our results are indicative of a functional segregation of P and K cells in V1 and adds relevant information to the debate of whether P and K pathways distinction is blurred at the level of V1. If V1 color-coding cells are organized in myriad ways and the distinction between P and K pathways is blurred after the first synapse in V1 (Sincich and Horton, 2005; Conway et al., 2010), tDCS should affect protan, deutan, and tritan discriminations in a similar way. Our results point to a different direction, suggesting that these pathways can be differentially affected by tDCS. The absence of anodal effects on red-green discrimination can be accounted for by a putative ceiling effect (that reflects functional differences between P and K pathways in V1). The qualitatively different cathodal effects on tritan and deutan discriminations could be accounted for by morphological, biophysical, or connectivity distinctions. Our results suggest a significant segregation between P and K pathways no matter if the determinants are in the molecular or systemic level. The present work shows that tDCS can affect sensory processing in a pathway-specific manner and is an adequate tool to explore the cortical organization of sensory functions.

The anodal tDCS effects on tritan and the cathodal tDCS effects on deutan thresholds tended to return to baseline after 15 min of the end of stimulation. This result is in line with the notion that tDCS has a more limited time course on sensory performance when compared to motor performance (Antal and Paulus, 2008). In addition, tDCS was only delivered once for each current direction in each participant. Current research suggests that in order to achieve stable and long-lasting tDCS effects, more than one session is needed (Zaghi et al., 2010; Brunoni et al., 2011). Future work using tDCS to modulate color perception should approach the issue of the necessary parameters to achieve long-lasting effects of tDCS on this modality. However, the inducement of long-lasting effects on color vision of healthy volunteer is controversial and with ethical implications. At the same time, our findings open an avenue of new investigations. Further studies should focus on the effects of tDCS on color vision defective patients both in terms of acute effect as well as long-lasting effects.

CONCLUSION

Our results showed that tDCS can modulate color perception in a pathway-specific robust manner, improving visual discrimination performance to levels that are above the normative values of healthy controls. This suggests that tDCS could have positive outcomes if used for color vision rehabilitation. The distinct effects of tDCS on protan, deutan, and tritan discriminations illustrate that tDCS is an effective tool for the investigation of the cortical organization of visual processing. tDCS had a qualitatively different effect on tritan and deutan discriminations, a result that suggests some level of segregation of P and K pathways within V1. This result adds relevant knowledge to the controversial matter of P and K integration in

V1. Future research should target other visual areas involved in color perception. Also, future research combining visual discrimination tasks and tDCS of visual areas should take into account the color parameters of stimuli as possible confounding factors.

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Neurobiological effects of transcranial direct current stimulation: a review

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Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that is affordable and easy to operate compared to other neuromodulation techniques. Anodal stimulation increases cortical excitability, while the cathodal stimulation decreases it. Although tDCS is a promising treatment approach for chronic pain as well as for neuropsychiatric diseases and other neurological disorders, several complex neurobiological mechanisms that are not well understood are involved in its effect. The purpose of this systematic review is to summarize the current knowledge regarding the neurobiological mechanisms involved in the effects of tDCS. The initial search resulted in 171 articles. After applying inclusion and exclusion criteria, we screened 32 full-text articles to extract findings about the neurobiology of tDCS effects including investigation of cortical excitability parameters. Overall, these findings show that tDCS involves a cascade of events at the cellular and molecular levels. Moreover, tDCS is associated with glutamatergic, GABAergic, dopaminergic, serotonergic, and cholinergic activity modulation. Though these studies provide important advancements toward the understanding of mechanisms underlying tDCS effects, further studies are needed to integrate these mechanisms as to optimize clinical development of tDCS.

Keywords: tDCS, neurobiology, neuromodulation, functional effects, long-term depression, long-term potentiation

INTRODUCTION

Transcranial Direct Current Stimulation (tDCS) has been utilized for the modulation of cortical excitability (Nitsche and Paulus, 2000; Fregni et al., 2005; Dieckhöfer et al., 2006; Nitsche et al., 2007; Wagner et al., 2007b) in various diseases, such as depression, chronic pain, stroke, and Parkinson's disease (Hansen et al., 2010; Lindenberg et al., 2010; Antal and Paulus, 2011; Borckardt et al., 2011, 2012; Riberto et al., 2011; DaSilva et al., 2012; Knotkova et al., 2012; Kumru et al., 2012). tDCS consists of applying direct current (DC) over the scalp using electrodes that are enclosed in perforated sponge pockets soaked with a saline solution or a rubber electrode with conductive gel (Vanneste et al., 2010; DaSilva et al., 2011). It effects depend on the following factors: the size, polarity and position of the electrodes, the applied current intensity, the density and duration of stimulation, and the properties of the tissue in the stimulated area.

This technique can induce long-lasting and polarity-specific changes in the excitability of the motor cortex in humans (Nitsche and Paulus, 2001; Lang et al., 2004). Depending on the current flow, it can increase or decrease neuronal excitability. The mechanisms are electrode-dependent and involve either (1) membrane depolarization (increased spontaneous firing and excitability of the cortical neurons for anodal stimulation) or (2) membrane hyperpolarization (decreased neuronal firing and excitability for cathodal stimulation; Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003a). In the most commonly used procedure, one electrode is placed over a specific site while the other reference electrode is placed over another location to complete the circuit of current flow. The electrode positioning is critical for determining the direction and spatial distribution of the current flow and, ultimately, the effectiveness of the treatment (Utz et al., 2010).

The exact pathways involved in the effects of tDCS are not fully understood (Wagner et al., 2007a; Utz et al., 2010; Stagg and Nitsche, 2011). Thus, more studies to support its clinical application are needed. It is known that weak fields are the basis of the biological effects of tDCS. It is thought that the application of an electric field with sufficient strength and duration can cause a rapid increase in the electrical conductance of biological membranes. This is associated with an increased permeability for ions and small and large molecules. However, the knowledge about the effects on neurotransmission, neurochemical markers, neural pathways, neural tracts, or neural interfaces is incomplete.

Few tDCS studies have been published that assess its underlying neurobiological mechanism. Thus, there is need for further studies to broaden our understanding of the possible neurochemical and neurobiological mechanisms involved. In addition, a better understanding of its possible mechanisms is essential to advance the research and to support its application in a clinical setting. Currently, there are only 123 clinical trials published in English using tDCS. We found 32 studies that assessed the some neurobiological mechanisms.

Neurophysiologists have shown great interest in investigating the effects of low-intensity electrical stimulation, in which the currents used are typically equal to or less than 2 mA, applied to humans (Zaghi et al., 2009). However, studies in human are sometimes insufficient to understand the underlying mechanisms. To address this, we use the translational approach of animal research. The purpose of this review is to summarize the current knowledge and to improve the understanding of the neurobiological mechanisms that may be involved in the effects of tDCS. Moreover, we aim to reveal novel insights into the mechanism of action of the observed clinical responses.

METHODS

This systematic review is based on a literature search using PubMed, Web of Science, OVID MEDLINE, and the Cochrane Library. The keyword "tDCS" was used in combination with other keywords such as "pain," "chronic pain," "depression," "Parkinson," "stroke," "cell mechanisms," "neurobiological mechanisms," "functional effects," "intracellular effects," "receptor," "long-term depression (LTD)," and "long-term potentiation (LTP)." The term "AND/OR" was used in each combination. The reference sections of the studies that met our inclusion criteria were also manually screened for relevant publications.

INCLUSION CRITERIA

Studies had to meet the following criteria: (1) published in English between 2002 and 2012, (2) report original research, (3) tDCS, (4) the main factors of interest were neurotransmitters, peptides, neurochemical markers, neural pathways, neural tracts, or neural interfaces, and (5) had outcome measures regarding changes in symptoms or electrophysiological or biochemical parameters. Full-text records of each retrieved article were reviewed to determine which studies would be included. We collected information regarding neurobiological mechanisms from human, animal, and cell-culture studies. Moreover, we extracted information on cortical parameters. We systematically screened all articles for the following information: experimental design, sample size, stimulation details (stimulation paradigm and parameters), and main results regarding neurobiological mechanisms. As this review is mainly focused on the neurobiology of tDCS effects, we did not conduct statistical analyses, but instead summarize the results in a narrative format. The exclusion criterion was a lack of original data, such as review articles.

RESULTS

The final search identified 171 studies. After applying the inclusion and exclusion criteria, we included 32 studies for full-text analysis. We screened the articles according to neurobiological mechanisms, and summarized the results separately for *in vivo* (humans and animals) and *in vitro* studies. **Tables 1–4** show the main findings.

NEUROBIOLOGICAL MECHANISMS

One of the most common ways that we can improve our understanding of neurobiological mechanisms is through pharmacological intervention. Numerous studies have attempted to understand the mechanism of action related to the tDCS neuromodulation technique (Liebetanz et al., 2002; Nitsche et al., 2006; Monte-Silva et al., 2009). It is important to note that these investigations include healthy volunteers as well as patients. In addition, *in vitro* studies and experimental research in animal models can help elucidate the possible mechanisms involved in tDCS.

In vivo – humans

A total of 20 articles reported tDCS experiments in humans. The results are presented in **Table 1**. Most of the articles used pharmacological interventions to characterize the after-effects of tDCS, some of them analyzing the short and long-lasting effects after tDCS. The use of drugs that interact in diverse systems, such as GABAergic, serotoninergic, and cholinergic, can contribute to clarify the some of the neurobiological mechanisms of action related to after-effects of tDCS. The results from these studies demonstrate that a variety of systems can be involved in the mechanisms of action of tDCS. All these articles investigated healthy subjects, except for one case report (Antal and Paulus, 2011).

In vitro

A total of six articles reported basic DC experiment. The results are given in **Table 2**. Studies *in vitro* can bring us the membrane and intracellular mechanisms involved in the effects of DC stimulation. The studies described that the intracellular calcium can be related to one pathway mechanism of tDCS. The BDNF-secretion may be other pathway that can explain the after-effects of DC stimulation.

In vivo – animals

A total of three articles reported DC stimulation experiments in animals. The results are summarized in **Table 3**. These results demonstrate that DC stimulation can promote neuroprotective or neuroplasticity effects in rat animal models. In addition, it was demonstrated modulation in the learning process after stimulation using rabbits.

CORTICAL EXCITABILITY

We included four articles that associated cortical excitability parameters with neurobiological mechanisms. The parameters of cortical excitability can contribute to a better understanding of the effects of neuromodulatory techniques, such as tDCS. Transcranial magnetic stimulation (TMS) is a tool that can be used for evaluating the parameters of cortical excitability in response to neurostimulatory interventions. The results demonstrated the polarity-specific response of tDCS, anodal stimulation increases MEPs and cathodal decreases it. Most of studies were performed in healthy subjects. The results are given in **Table 4**.

Table 1 | Neurobiological mechanisms: human *in vivo* studies ($N = 20$).

Author (year)	Title	Experiment	*N*	Intervention	Results/insights
Liebetanz et al. (2002)	Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability	tDCS 1 mA (5 min) anodal or cathodal over left M1	11 right-handed healthy subjects (8 male)	Carbamazepine (CBZ), dextromethorphan (DMO), or placebo	DMO induced a suppression of the after-effects of both anodal and cathodal stimulation. CBZ eliminated only the anodal effects
Nitsche et al. (2003b)	Pharmacological modulation of cortical excitability shifts. Induced by transcranial direct current stimulation in humans	tDCS 1 mA, cathodal (4 s, 9 min), or anodal tDCS (11–13 min) over left M1	11–14 healthy subjects	Carbamazepine, flunarizine (FLU), dextromethorphan, or placebo	CBZ eliminated only the anodal effects during and after tDCS. FLU has similar effects. The DMO results were similar to those observed in a previous study
Nitsche et al. (2004a)	GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans	tDCS 1 mA cathodal (4 s, 5 min, and 9 min) or anodal (11 min) over left M1	6–12 healthy subjects	Lorazepam (LOR) or placebo	LOR promoted a delayed, enhanced, and prolonged increase of excitability induced by anodal tDCS
Nitsche et al. (2004b)	Consolidation of human motor cortical neuroplasticity by d-cycloserine	tDCS 1 mA, cathodal (9 min) or anodal (13 min) over left M1	12 healthy subjects (5 male)	d-cycloserine (d-CYC) or placebo	d-CYC selectively potentiated the duration of increased excitability induced by anodal tDCS
Nitsche et al. (2004c)	Catecholaminergic consolidation of motor cortical neuroplasticity in humans	tDCS 1 mA, cathodal (4 s, 7 min, or 9 min) and anodal (13 min)	5–12 healthy subjects	Amphetaminil (AMP), propanolol (PRO), amphetaminil/ dextromethorphan (DMO), or placebo	AMP enhanced and prolonged the increase of the long-lasting excitability changes after anodal tDCS. DMO/AMP blocked any enhancement induced by anodal tDCS. PRO diminished the duration of the after-effects of anodal and cathodal tDCS
Nitsche et al. (2006)	Dopaminergic modulation of long-lasting direct current stimulation of the human motor cortex	tDCS 1 mA, cathodal (9 min), or anodal (13 min) over left M1	4–12 healthy subjects	Sulpiride (SUL), sulpiride/pergolide (PGL), or placebo	SUL almost completely abolished the after-effects of anodal and cathodal tDCS, and promoted a delay in the increase of excitability after anodal tDCS. SUL/PGL did not re-establish the changes induced by tDCS, abolished the delayed excitability increase after anodal tDCS, and prolonged the excitability decrease after cathodal tDCS
Kuo et al. (2007)	Focusing effect of acetylcholine on neuroplasticity in the human motor cortex	tDCS 1 mA, cathodal (9 min), or anodal (13 min) over left M1; followed by iPAS or ePAS	10–12 healthy subjects	Rivastigmine (RIVA) or placebo	RIVA blocked the induction of excitability enhancement after anodal tDCS, showed a tendency to first reduce the inhibition by cathodal tDCS and then later to stabilize the induced inhibition, and enhanced and prolonged the excitability enhancement produced by ePAS and the excitability diminution induced by iPAS

(Continued)

Table 1 | Continued

Author (year)	Title	Experiment	*N*	Intervention	Results/insights
Cheeran et al. (2008)	A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS	cTBS, iTBS, cathodal tDCS 1 mA (10 min), 1 Hz rTMS, PAS	61 healthy volunteers		Individuals with polymorphism Val66 Met did not present the homeostatic effect expected after pre-conditioning with cathodal tDCS following by 1 Hz rTMS
Kuo et al. (2008)	Boosting focally induced brain plasticity by dopamine	tDCS 1 mA, anodal (13 min), or cathodal (9 min) over left M1	7–11 healthy subjects	Levodopa (l-dopa) or placebo	l-dopa turned the unspecific excitability enhancement caused by anodal tDCS into inhibition, prolonged the excitability diminution induced by cathodal tDCS, and stabilized the PAS-induced synapse-specific excitability increase
Rango et al. (2008)	Myoinositol content in the human brain is modified by transcranial direct current stimulation in a matter of minutes: a ^{1}H-MRS study	tDCS 1.5 mA (15 min) anodal or sham over right M1	10 healthy subjects (6 males)		Anodal tDCS increased the myoinositol up to 30 min after stimulation, but only below the electrode
Terney et al. (2008)	Pergolide increases the efficacy of cathodal direct current stimulation to reduce the amplitude of laser-evoked potentials in humans	tDCS cathodal 1 mA (15 min) or control over M1	12 healthy volunteers (5 male)	Pergolide (PGL) or placebo	PGL prolonged the cathodal after-effects, including the reduction of the N2 component for up 2 h and the reduction in pain sensation for up to 40 min
Monte-Silva et al. (2009)	Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and non-focal plasticity in humans	tDCS 1 mA, anodal (13 min), cathodal (9 min), or sham over left M1; followed by iPAS or ePAS	12 healthy volunteers (6 male)	Ronipirole (RP) or placebo	RP produced an inverted "U" shaped dose-response curve in facilitatory plasticity after tDCS and ePAS and showed the same effect for inhibitory plasticity after tDCS only
Nitsche et al. (2009a)	D1-receptor impact on neuroplasticity in humans	tDCS 1 mA, anodal (13 min), cathodal (9 min) over left M1; followed by iPAS or ePAS	10–12 healthy subjects	Sulpiride (SULP), levodopa (l-dopa)/sulpiride or placebo	SULP abolished the inhibition induced by iPAS, without effecting facilitatory ePAS. l-dopa was able to re-establish the inhibition induced by iPAS
Nitsche et al. (2009b)	Serotonin affects transcranial direct current-induced neuroplasticity in humans	tDCS 1 mA, anodal (13 min), or cathodal (9 min)	12 healthy subjects (8 male)	Citalopram (CIT) or placebo	CIT enhanced and prolonged the facilitation induced by anodal tDCS, whereas it turned cathodal tDCS-induced inhibition into facilitation
Stagg et al. (2009)	Polarity sensitive modulation of cortical neurotransmitters by transcranial stimulation	tDCS 1 mA and anodal, cathodal, or sham (10 min)	7–11 healthy subjects		Anodal tDCS resulted in a local reduction of GABA transmitter, while cathodal tDCS resulted in a decreased glutamate level, which correlated with a reduction in GABA levels

(Continued)

Table 1 | Continued

Author (year)	Title	Experiment	*N*	Intervention	Results/insights
Monte-Silva et al. (2010)	Dosage-dependent non-linear effect of l-dopa on human motor cortex plasticity	tDCS 1 mA, anodal (13 min), or cathodal (9 min) over left M1	12 right-handed healthy subjects (5 men)	Levodopa (l-dopa) or placebo	Low and high doses of l-dopa abolished the facilitatory and inhibitory effects of tDCS
Stagg et al. (2011)	The role of GABA in human motor learning	tDCS 1 mA (10 min) over left M1	12 right-handed healthy subjects (6 males)		A positive correlation was observed between the GABA decrease after anodal tDCS, the degree of motor learning, and the degree of fMRI signal change within the left M1 during learning
Thirugnanasambandam et al. (2011)	Nicotinergic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans	tDCS 1 mA, anodal (13 min), or cathodal (9 min) over left M1	48 healthy volunteers	Nicotine patch or placebo patch	Nicotine abolished or reduced the inhibitory plasticity after iPAS and cathodal tDCS and the facilitatory plasticity induced by anodal tDCS. The focal facilitatory plasticity (ePAS) was slightly prolonged by nicotine
Antal and Paulus (2011)	A case of refractory orofacial pain treated by transcranial direct current stimulation applied overhand motor area in combination with NMDA agonist drug intake	1st visit: anodal tDCS 1 mA (20 min) for 5 days 2nd visit: cathodal 2 mA (20 min) for 5 days at 2 mA; both over M1	1 female patient with persistent orofacial pain	d-cycloserine	The d-cycloserine combined with anodal tDCS resulted in a 60% reduction in pain perception as well as a significant level of pain relief sensation for up to 6 weeks
Chaieb et al. (2012)	Pharmacological modulation of the short-lasting effects of antagonistic direct current stimulation over the human motor cortex	tDCS 1 mA, 10 min (5 min anodal–5 min cathodal or vice-versa) over left M1	8 healthy subjects (6 male)	d-cycloserine (d-CYC), pergolide (PGL), or placebo	The second stimulation produced increases in excitability following anodal stimulation and inhibition following cathodal stimulation. After d-CYC, only inhibition was observed (for both the cathodal-anodal and anodal-cathodal stimulation)

iPAS, inhibitory paired associative stimulation; ePAS, excitatory paired associative stimulation; cTBS, continuous theta burst; iTBS, intermittent theta burst; rTMS, repetitive magnetic stimulation; PAS, paired associative stimulation; N2 component, negative wave approximately 200 ms as revealed by event-related-potentials measured by electroencephalography.

Table 2 | Neurobiological mechanisms: *in vitro* studies (*N* = 6).

Author (year)	Title	Experiment	*N*	Model	Results/insights
Khatib et al. (2004)	Physiologic electrical stimulation provokes intracellular calcium increase mediated by phospholipase C activation in human osteoblasts	Electrical stimulation, 2 V/cm	Cells at 60–70% confluence	Osteoblasts cell culture	Electrical stimulation promoted an increase in $[Ca^{2+}]_i$ that showed a partial inhibition after blocking cation channels or chelating $[Ca^{2+}]_i$. A phospholipase C inhibitor completely abolished the $[Ca^{2+}]_i$ increase
Radman et al. (2009)	Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation *in vitro*	DC stimulation, anodal ∼5 mV/mm up to ∼±30 mV/mm	Coronal slices (300 μm) of primary motor cortex (M1) −51 neurons (Pyramidal cells)	Tissue model	The cells responded to DC in a subthreshold and suprathreshold uniform electric field. The importance of the morphology and type of cell in mediating the response to the stimulus was discussed
Fritsch et al. (2010)	Direct stimulation promotes BDNF-dependent synaptic plasticity: potential implication for motor learning	DC stimulation 10 μA	Not described	Coronal mouse slices	They proposed that DCS could induce synaptic plasticity *in vitro* in brain regions that do not respond to conventional protocols. This was dependent on enhanced BDNF-secretion and TrkB-activation
Dubé et al. (2012)	Human keratinocytes respond to direct stimulation by increasing intracellular calcium: preferential response of poorly differentiated cells	Electrical field of 200 mV/mm	The cells were plated into six wells culture dishes) cells/cm^2 and cultured until 80% confluence was reached	Keratinocytes cell culture	Stimulation induced an increase in intracellular $[Ca^{2+}]$. The extracellular calcium was responsible for this increase, and it was mediated in part by L-type voltage-gated calcium channels. The increase was only detected in involucrin-negative keratinocytes
Ruohonen and Karhu (2012)	tDCS possibly stimulates glial cells	DC stimulation in E-field – 2-mA current for tDCS – 20 mV (2 mA/50 mA) = 0.8 mV	Theoretical analysis	Glial cells	They considered the possibility of glial mechanisms could be modulated by tDCS
Ranieri et al. (2012)	Modulation of LTP at rat hippocampal CA3–CA1 synapses by direct current stimulation	DCS anodal or cathodal, 50 stimuli at 100 Hz (500 ms each) repeated every 20 s	Not described	Hippocampal slices from male Wistar rats	They suggested that tDCS can modulate LTP in intact human brain

DC, direct current stimulation; $[Ca^{2+}]_i$, calcium intracellular; BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase B; LTP, long-term potentiation.

DISCUSSION

Overall, we reviewed 32 articles in full-text extracting the main findings of tDCS on neurobiological mechanisms. TDCS effects appear to be multifactorial and capable to induce changes in different systems. Thus, the effects underlying tDCS cannot be simplified to only one mechanism. tDCS induces physiological changes that result in local and distant plastic changes. Some of the tDCS effects seem to be associated with homeostatic effects in a facilitatory and/or inhibitory way.

The studies reviewed in this article demonstrate that the plastic changes induced by tDCS involve regulation of a broad variety of neurotransmitters including dopamine, acetylcholine, and serotonin (Kuo et al., 2007; Monte-Silva et al., 2009; Nitsche et al., 2009b), and also affect a variety of different neuronal membrane channels, such as sodium and calcium. Furthermore the induction of tDCS after-effects is associated with synaptic modulation. The after-effects of anodal and cathodal tDCS are influenced by the potentiation of synaptic glutamatergic receptors (Nitsche et al., 2003b). Furthermore, anodal tDCS is also influenced by GABAergic neurotransmission via interneurons (Nitsche et al., 2004a).

We showed several consistent pharmacological approaches to understand the mechanisms of tDCS (**Table 1**). The DMO (a NMDA-receptor antagonist) induces suppression of the

Table 3 | Neurobiological mechanisms: *in vivo* animals (*N* = 3).

Author (year)	Title	Experiment	*N*	Results/insights
Kim et al. (2010)	Functional and histological changes after repeated transcranial direct current stimulation in a stroke model	Anodal or cathodal tDCS, 0.1 mA for 30 min for 2 weeks	41 Sprague-Dawley rats	Anodal stimulation showed a neuroprotective effect (functional improvement and well-preserved white matter axons)
Márquez-Ruiz et al. (2012)	Transcranial direct current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits	Anodal or cathodal tDCS from 0.5 to 2 mA (immediate effects) and 1 mA for 20 min (after-effects) over somatosensory (S1) cortex	13 rabbits	Associative learning is modulated by tDCS. Changes were observed in the amplitude and area of the S1 components following anodal or cathodal stimulation. tDCS modulates paired-pulse responses. LTD evoked in the somatosensory cortex after cathodal tDCS is prevented by blocking adenosine A1 receptors
Yoon et al. (2012)	Functional improvement and neuroplastic effects of anodal transcranial direct current stimulation (tDCS) delivered 1 day vs. 1 week after cerebral ischemia in rats	Anodal or sham tDCS, 0.2 mA for 20 min for 5 days	30 male Sprague-Dawley rats	Anodal tDCS modulated neural plasticity around the ischemic penumbra and even in the contralesional area without aggravating the infarction volume or causing metabolic alterations

LTD, long-term depression.

Table 4 | Cortical parameters (*N* = 4).

Author (year)	Title	Experiment	*N*	Results/insights
Lang et al. (2004)	Effects of tDCS stimulation over the human motor cortex on corticospinal and transcallosal excitability	tDCS 1 mA anodal or cathodal (10 min) over left M1	8 right-handed healthy subjects (5 male)	Increased or decreased MEPs according to the specific polarity in the left hemisphere. The duration of TC evoked from the right M1 was shortened or prolonged according to the specific polarity
Hasan et al. (2011)	Dysfunctional long-term potentiation-like plasticity in schizophrenia revealed by tDCS	tDCS 1 mA (3 min) anodal over left M1	44 individuals (22 paranoid schizophrenia were compared with 22 matched healthy subjects)	Anodal tDCS resulted in a reduction in LTP-like plasticity in multi-episode schizophrenia patients compared to recent-onset schizophrenia patients and healthy controls. All schizophrenia patients demonstrated reduced cortical inhibition
Polanía et al. (2011)	Introducing graph theory to track for neuroplastic alterations in the resting human brain: a tDCS study	tDCS 1 mA (10 min) anodal or sham over left M1	13 healthy volunteers (6 male)	Anodal tDCS increased the nodal minimum path lengths in the left somatomotor (SM1) cortex, i.e., the number of direct functional connections from the left SM1 to the topologically distant gray matter voxels was significantly decreased. The functional coupling between the premotor and superior parietal areas with the left SM1 was significantly increased. The nodal connectivity degree in the left posterior cingulated cortex area and in the right DLPFC was significantly increased
Scelzo et al. (2011)	Increased short latency afferent inhibition after anodal tDCS	tDCS 1 mA (13 min) anodal over primary motor cortex	12 subjects (4 male)	Anodal tDCS promoted increased short latency afferent inhibition (SAI), which can be related to central cholinergic interneuronal circuits

M1, primary motor cortex; MEPSs, motor evoked potentials; TC, transcallosal inhibition; LTP, long-term potentiation; DLPFC, dorsolateral prefrontal cortex.

after-effects of both anodal and cathodal stimulation (Liebetanz et al., 2002), while the CBZ (a sodium use-dependent channel blocker) eliminates only the anodal effects (Liebetanz et al., 2002). Similar effect was observed using flunarizine (a calcium channel blocker) in the study of Nitsche et al. (2003c); however with smaller magnitude of effects as compared with carbamazepine. Lorazepam (a GABAergic agonist) and D-cycloserine (D-CYC, a partial NMDA agonist) selectively potentiate the effects of anodal DC with increased excitability (Nitsche et al., 2004a,b). Propranolol (a non-selective β-adrenergic antagonist) decreases the

duration of the after-effects of anodal and cathodal stimulation (Nitsche et al., 2006). These data demonstrate the involvement of multiple neurotransmitter functions in the mechanisms of action of tDCS.

Therefore one important concept when understanding the effects of tDCS is to understand that its initial effect on inducing neuronal depolarization or hyperpolarization(Creutzfeldt et al., 1962; Bindman et al., 1964) results also in lasting effects characterized by LTP and LTD like effects (Hattori et al., 1990; Moriwaki, 1991; Islam et al., 1995; Paulus, 2004). These mechanisms are supported by clinical findings, such as enhanced in the learning and antidepressant effects using tDCS over several weeks (Fregni et al., 2006; Boggio et al., 2008; Loo et al., 2010; Brunoni et al., 2011). Overall, these studies provide valuable insights into the mechanisms of action that tDCS exerts on neuronal tissue (for a review, see Nitsche, 2005).

This systematic review also highlights that the anodal effects are associated with modulation of GABAergic interneurons (Nitsche et al., 2004a; Stagg et al., 2009; Stagg and Nitsche, 2011). This effect is evidenced by the effects of tDCS on short-interval intracortical inhibition and intracortical facilitation (Nitsche et al., 2005; Stagg et al., 2009; Stagg and Nitsche, 2011). Given that GABAergic cortical inhibitory interneurons play a role in the early stage of Alzheimer's disease (Koliatsos et al., 2006), modulation of these interneurons by tDCS is a potential disease-modifying mechanism. Also, a previous magnetic resonance spectroscopy (MRS) study found that tDCS reduces GABA cortical concentrations and this effect is correlated with impaired glutamatergic neuronal activity (Stagg et al., 2009). These tDCS effects reduce the imbalance between these excitatory and inhibitory neurotransmitter systems. In contrast, carbamazepine selectively eliminated the anodal effects, suggesting that the anodal tDCS require initially depolarization of neuronal membrane potentials (Liebetanz et al., 2002). Liebetanz et al. (2002) provided pharmacological evidence that the induction of the after-effects of tDCS requires a combination of glutamatergic and membrane mechanisms, similar to the induction of established types of short or long-term neuroplasticity.

An important concept when considering the mechanism of TDCS is its association with other interventions such as behavioral and/or pharmacological interventions. The combined application of cathodal/anodal tDCS and D-CYC (a partial agonist of NMDA receptors) during a motor learning task showed that the excitability diminution induced by cathodal tDCS prior to motor learning, or an excitability enhancement induced by anodal tDCS combined with D-CYC, impairs learning performance. Neurophysiologically, a decrease in MEP amplitude was observed (Chaieb et al., 2012). In studies combining tDCS with pharmacological interventions, authors found that application of nicotine patch reduces both inhibitory plasticity after cathodal tDCS and the facilitatory plasticity induced by anodal tDCS (Thirugnanasambandam et al., 2011), while acetylcholine enhances the synapse-specific cortical excitability after anodal tDCS (Kuo et al., 2007). In addition, the inhibitory effect of rivastigmine (a cholinesterase inhibitor) on neuroplasticity induced by anodal tDCS seems contradictory to the results obtained from animal studies in which LTP was facilitated by cholinergic stimulation (Brocher et al., 1992; Abe et al., 1994; Hasselmo and Barkai, 1995; Patil et al., 1998; Kuo et al., 2007). However, these different results might be due to methodological difference between these studies. It is possible that synapses that are globally modified by tDCS are more susceptible to cholinergic suppression of synaptic transmission during plasticity induction.

Other neuropsychotropic drugs showed similar modulation of tDCS-induced plasticity. In fact, TDCS effects are shortened by propranolol following 13 min of anodal and 9 min of cathodal tDCS but does not eliminate those (Nitsche et al., 2004c). Moreover, β-adrenergic receptor stimulation may have an important role for the effects of amphetaminil (a precursor of amphetamine) to increase the consolidation of externally induced excitability enhancements. Similar to results obtained for the β-adrenergic receptor in the hippocampus, it has been also shown that dopamine via the D1-receptor facilitates NMDA-dependent excitability and facilitates NMDA-dependent LTP through Cyclic-adenosine-monophosphate-dependent (cAMP) mechanisms (Otmakhova and Lisman, 1996, 1998; Bailey et al., 2000). Furthermore, it was shown that a single administration of amphetaminil induces prominent and long-term enhancements of cortical dopamine signaling (Vanderschuren et al., 1999). In this way, prolonged dopaminergic activation could stabilize the tDCS-induced NMDA-receptor-dependent excitability enhancements.

Additionally, tDCS promotes changes in brain-derived neurotrophic factor (BDNF; Fritsch et al., 2010). The BDNF promotes the survival of neurons (Lefaucheur, 2008a,b) and is important for cell proliferation (Tessarollo, 1998). Given the results from the study of Cheeran et al. (2008) demonstrating that a common polymorphism in the BDNF gene modulates human cortical plasticity, BDNF could be a marker (and potentially also a pathway) for assessing the effects of tDCS on the nervous system.

Also, new approaches, such as BOLD fMRI, can provide critical information on the mechanisms of tDCS. Furthermore, assessments during the execution of tasks or tDCS stimulation both alone and in combination with other interventions can provide new insights into tDCS effects. Overall, there are many neuropharmacological and neurophysiological methods that can improve our understanding in the neurobiological mechanisms involved in the therapeutic effects of tDCS intervention.

LIMITATIONS IN THE CURRENT KNOWLEDGE

Although tDCS is one of the most investigated techniques of non-invasive brain stimulation, there are relatively few studies investigating the neurobiological mechanisms associated with the tDCS (**Tables 1–4**). This article provides information regarding mechanisms of action of tDCS, however most of the mechanistic literature investigated tDCS-related neuroplasticity in the motor cortex. Although motor cortex related data may be of some relevance for treatment of disorders such as chronic pain and motor rehabilitation after stroke where the targeted area is M1, results from experiments in this area are less relevant for other critical targets such as dorsolateral prefrontal cortex. Further research is needed to determine if mechanisms found in studies investigating M1 are also relevant to brain target regions.

Another important issue that has not been adequately addressed is whether the neurophysiological findings can be translated into clinical effects. For instance, whether an increase in excitability induced by anodal tDCS translates into increased motor consolidation. Further larger studies need to address this important question. Finally, it is also important the impact of parameters of stimulation in neuroplasticity – i.e., whether longer periods of stimulation lead to beneficial or harmful effects and also to understand the interaction of tDCS with pharmacological treatment in real clinical practice where patients are taking several medications simultaneously.

CONCLUSION AND PERSPECTIVES

In this review, we discuss the mechanisms of the action of tDCS as to understand neurobiology and cell-signaling pathways associated with tDCS effects. Although initial tDCS studies, showed that its effects are related to the intensity, polarity, and duration of stimulation and the brain region stimulated, it is still not clear the optimal parameters of stimulation especially given the dynamic changes of brain excitability. Recent studies in animal and cell models have suggested that tDCS induces plasticity, neuronal viability, neuronal morphology, modulates synaptic transmission, and biosynthesis of molecules. TDCS induces a cascade of events associated with glutamatergic, GABAergic, dopaminergic, serotonergic, and cholinergic activity modulation. In addition, we also show the importance of conducting both experimental and clinical studies to understand tDCS-induced neuroplasticity. Overall, compelling evidence from studies reviewed in this article emphasizes possible approaches to understand the neurobiology of tDCS mechanisms. Additionally, it opens new possibilities for future tDCS research in basic and clinical neuroscience.

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Behavioral and electrophysiological effects of transcranial direct current stimulation of the parietal cortex in a visuo-spatial working memory task

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Impairments of working memory (WM) performance are frequent concomitant symptoms in several psychiatric and neurologic diseases. Despite the great advance in treating the reduced WM abilities in patients suffering from, e.g., Parkinson's and Alzheimer's disease by means of transcranial direct current stimulation (tDCS), the exact neurophysiological underpinning subserving these therapeutic tDCS-effects are still unknown. In the present study we investigated the impact of tDCS on performance in a visuo-spatial WM task and its underlying neural activity. In three experimental sessions, participants performed a delayed matching-to-sample WM task after sham, anodal, and cathodal tDCS over the right parietal cortex. The results showed that tDCS modulated WM performance and its underlying electrophysiological brain activity in a polarity-specific way. Parietal tDCS altered event-related potentials and oscillatory power in the alpha band at posterior electrode sites. The present study demonstrates that posterior tDCS can alter visuo-spatial WM performance by modulating the underlying neural activity. This result can be considered an important step toward a better understanding of the mechanisms involved in tDCS-induced modulations of cognitive processing. This is of particular importance for the application of electrical brain stimulation as a therapeutic treatment of neuropsychiatric deficits in clinical populations.

Keywords: tDCS, TES, working memory, parietal cortex, EEG, working memory capacity, alpha

INTRODUCTION

Working memory (WM) refers to a mental workspace that allows one to temporally store and manipulate a limited amount of information in mind. WM functioning is essential for a wide range of complex cognitive tasks, such as reasoning, problem solving, language comprehension, and learning (Baddeley, 1992). WM performance typically activates a fronto-parietal network, including the dorsolateral prefrontal cortex (DLPFC; Smith and Jonides, 1997; Courtney et al., 1998; Nystrom et al., 2000; Hautzel et al., 2002) and the posterior parietal lobe (Owen et al., 2005). While the DLPFC is involved in the processing of stimulus information during retention times (Funahashi et al., 1993), the parietal cortices are responsible for the storage of perceptual attributes (Callicott et al., 1999), and the maintenance of information specifically regarding spatial locations (Olson and Berryhill, 2009) hereby constituting the capacity limit for the amount of items an individual is able to store (Todd and Marois, 2004). Consequently, the involvement of the posterior parietal lobe is consistently found during a wide range of WM tasks (Wager and Smith, 2003). Accordingly, damage of the posterior parietal lobe leads to WM impairments (Olson and Berryhill, 2009).

Impairments of WM performance are frequent concomitant symptoms in several psychiatric and neurologic diseases. Patients suffering from Alzheimer's disease (AD) exhibit specific deficits in visual and spatial WM performance. They demonstrate serious impairments of spatial memory span and the retention of visual information (Huntley and Howard, 2010). Specifically, the spatial WM component seems to be more strongly affected in AD compared to individuals with mild cognitive impairment (Alescio-Lautier et al., 2007). Likewise, patients with Parkinson's disease (PD) demonstrate a remarkable reduction in visuo-spatial WM abilities (Lees and Smith, 1983). In particular, these patients exhibit diminished storage capacities accompanied with deficits in retaining spatial, visual, and verbal information (Owen et al., 1997; Lee et al., 2010). Moreover, patients with amyotrophic lateral sclerosis (ALS) show reduced WM abilities associated with reduced spatial WM capacity (Hammer et al., 2011). In addition to neurological patient populations, psychiatric patients widely display specific WM impairments such as comprehensive visual WM abnormalities in patients with schizophrenia (Barch et al., 2003) and depression (Rose and Ebmeier, 2006).

Even though the administration of dopamine agonists has been shown to improve WM in normal subjects and patients with traumatic brain injury (TBI; McAllister et al., 2011; Wallace et al., 2011), the success of pharmacological treatments of WM-deficits is still restricted in terms of limited effectiveness and side-effects (Birks, 2006; Marder, 2006; McGurk et al., 2007). In recent years, transcranial direct current stimulation (tDCS) has been employed as a new approach to alter memory performances in healthy participants as well as to improve abnormal memory abilities

in neuropsychiatric patients (Brunoni et al., 2011; Nitsche and Paulus, 2011).

Transcranial direct current stimulation is a non-invasive technique for delivery of low currents to the cerebral cortex that results in the modulation of cortical excitability (Bindman et al., 1962). With tDCS, weak constant electric currents are applied on the cortical surface in a non-invasive and painless manner (Priori, 2003; Fox, 2011). The current flows between an active and a reference electrode. While a part of this current is shunted through the scalp, the rest is delivered to the brain tissue (Miranda et al., 2006), thereby inducing diminutions or enhancements of cortical excitability (Nitsche et al., 2008). The direction of the tDCS-induced effect depends on the current polarity. Anodal tDCS typically has an excitatory effect while cathodal tDCS decreases the cortical excitability in the region under the electrode (Nitsche and Paulus, 2000; Nitsche et al., 2003). Specifically, anodal tDCS causes a depolarization of the resting membrane potential and increases the firing rate, whereas cathodal tDCS decreases the firing rate via hyperpolarization of the resting membrane potential (Bindman et al., 1962; Purpura et al., 1965). Importantly, tDCS effects are not restricted to this primary polarization mechanism during stimulation, because after-effects persist over minutes to hours. These after-effects of tDCS are associated with a number of different mechanisms, including local changes in ionic concentrations (hydrogen, calcium) and levels of cyclic adenosine monophosphate (cAMP; Hattori et al., 1990), alterations in protein synthesis, and modulation of *N*-methyl-D-aspartate (NMDA) receptor efficacy (Gartside, 1968; Hattori et al., 1990; Liebetanz et al., 2002).

To date, the neuromodulatory changes induced by tDCS have been associated with modifications of the motor (Priori et al., 1998; Nitsche and Paulus, 2000) as well as a variety of sensory systems, including the visual (Antal et al., 2003, 2004; Accornero et al., 2007), the somatosensory (Dieckhofer et al., 2006; Antal et al., 2008), and the auditory system (Vines et al., 2006; Loui et al., 2010; Zaehle et al., 2011a). In the cognitive domain, polarity-specific effects of tDCS have been reported for WM functions in healthy participants (Fregni et al., 2005; Ohn et al., 2008; Zaehle et al., 2011b). Anodal tDCS over the DLPFC improves visual WM (Fregni et al., 2005; Zaehle et al., 2011b), whereas cathodal stimulation of the DLPFC interferes with short-term auditory memory performance (Elmer et al., 2009) and cathodal tDCS over the right inferior parietal cortex impairs object recognition WM (Berryhill et al., 2010). Regardless of polarity, tDCS over the cerebellum disrupts practice-dependent improvement during a verbal WM performance (Ferrucci et al., 2008b), whereas bifrontal tDCS impairs response selection and preparation in a verbal WM task (Marshall et al., 2005).

Most importantly, in addition to the progress of tDCS-related treatments of several cognitive (Fregni et al., 2006; Monti et al., 2008), affective (Boggio et al., 2008; Nitsche et al., 2009), and motor (Boggio et al., 2007; Bolognini et al., 2009) symptoms in neuropsychiatric disorders, first successful attempts in the direct modulation of specific memory deficits in neuropsychiatric patient populations have been demonstrated (Brunoni et al., 2011). It has been shown that idiopathic Parkinson patients could increase accuracy in a three-back letter WM task by approximately 20% during 20 min of 2 mA anodal tDCS over the left DLPFC (Boggio et al., 2006). Analogously, in stroke patients Jo et al. (2009) demonstrated enhanced recognition accuracy by approximately 10% in a verbal WM task after 30 min of 2 mA anodal tDCS over the left DLPFC. Moreover, in patients with AD 30 min anodal tDCS at 2 mA over left temporal and left DLPFC could increase recognition memory by 18.03 and 13.8%, respectively (Boggio et al., 2009). Similarly, in this patients word recognition memory could be improved by approximately 15% after 15 min anodal tDCS at 1.5 mA over tempo-parietal regions (Ferrucci et al., 2008a). Finally, bilateral anodal tDCS over the temporal cortex of AD patients at five consecutive days improves the visual recognition memory by 8.99% for at least 4 weeks (Boggio et al., 2011). However, the nature of the neurophysiological mechanisms underlying this tDCS-related cognitive enhancement is not well understood. In a recent study, we investigated the impact of tDCS over the left DLPFC on performance in a WM task and its underlying neural activity in healthy participants (Zaehle et al., 2011b). The anodal tDCS improved, whereas cathodal tDCS interfered with WM performance. These tDCS-induced effects were reflected in the neural oscillatory activity, showing polarity-specific alterations as a function of tDCS. Anodal tDCS enhanced, whereas cathodal tDCS suppressed the event-related oscillatory power in the theta and alpha range.

In the present study we examined the impact of tDCS on visuo-spatial WM performance and the underlying neural activity. In particular, we explored the effect of tDCS applied over the right parietal lobe on electrophysiological brain activity during a delayed matching-to-sample WM task. Given the critical involvement of the posterior parietal lobe in WM functions (Todd and Marois, 2004; Corbetta et al., 2008; McNab and Klingberg, 2008), we hypothesized tDCS-dependent alteration of WM performance. Furthermore, we predicted tDCS-related modifications of the underlying neural activity. To our knowledge, this is the first study to investigate the modulatory effects of parietal tDCS on electrophysiological brain activity in the context of a visuo-spatial WM task.

MATERIALS AND METHODS

PARTICIPANTS

Twelve healthy adults participated in this study (seven female). The age range was 21–31 years (mean 25.8 years). All subjects reported being consistent right-handers, having no metallic implant, no history of neuropsychiatric disorder, and normal or corrected-to-normal vision acuity and color vision.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Participants were seated comfortably in a recliner in front of a personal computer screen in an electromagnetically shielded room. The current was applied by a battery-driven DC-stimulator (Eldith, NeuroConn GmbH, Germany) using a pair of rubber electrodes in 5×7 cm synthetic sponges soaked in 0.9% NaCl solution. For stimulation of the right parietal cortex the active electrode (to which the term anodal/cathodal stimulation refers) was placed over P8/P10 and the reference electrode over P7/P9. These electrode positions were consistent to the European 10–20 system for electroencephalography (EEG) electrode placement

(Jasper, 1958). Each participant performed three separate tDCS sessions: one anodal, one cathodal, and one sham tDCS session separated by at least 24 h to avoid carry-over effects. The session order was counterbalanced across participants. Within each session, a constant current of 1 mA was applied for 30 min, with a linear fade in/fade out of 10 s. For sham stimulation the electrodes were placed on same positions, but after a fade in period of 10 s the stimulator was turned off without awareness of the participants. This procedure ensured that in the sham and stimulation conditions, participants experienced the initial itching that recedes over the first seconds of tDCS. Accordingly, none of the participants were able to determine whether or not they received real or sham stimulation.

WORKING MEMORY ASSESSMENT

The procedure of the experimental sessions was carried out sequentially: the participants performed a delayed matching-to-sample visuo-spatial WM task (Vogel and Machizawa, 2004) with concurrent EEG recording starting 7.4 min ± 2.4 (SD) after each tDCS condition (sham, anodal, cathodal). Stimulus presentation was controlled by the *Presentation* software (Neurobehavioral Systems, USA). During each trial, subjects were presented a fixation cross (2800 ± 3500 ms) followed by an arrow (200 ms) indicating the hemifield (left/right) to be attended. A memory array was then presented within two rectangular regions that were centered to the left and right on a gray background. These two rectangular regions of the memory arrays consisted of four colored circles (0.69°) with randomized position (within a rectangle) and were randomly colored (blue, brown, green, red, cyan, yellow, orange, pink, black, white). The memory array appeared for 150 ms and was followed by a retention period of 2000 ms during which subjects had to retain the memory array. This was followed by the presentation of a test array with one circle in the center of the screen, which was either identical or different in color compared to the circles shown in the memory array (cf. **Figure 1**). Subjects had 2000 ms before the onset of the next trial to make a push-button response to indicate whether or not the probe stimulus in the test array was identical to one stimulus in the memory array. The test sequence consisted of 256 trials separated into four runs. The order of the trials was identical across individual sessions but pseudo randomized across subject.

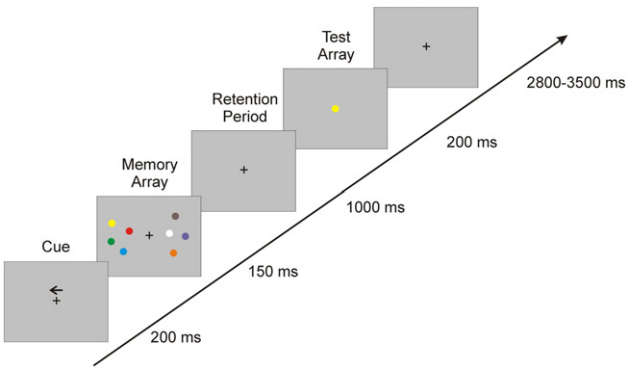

FIGURE 1 | Experimental design: the figure illustrates the sequence of events in each trial.

To assess the individual WM performance, we calculated the WM capacity K (Cowan's coefficient; Cowan, 2001) for each tDCS stimulation condition (sham, anodal, cathodal). Values for K were estimated for each subject by $K = S\,(H–F)$. The formula assumes, that if K items can be held in WM from an array of S objects, the probed item would have been one of those held in memory on K/S of the trials such that performance will be correct on K/S of the change trials (=hit rate H). To correct for guessing, this procedure also takes into account the false alarm rate F.

In the end, K values were analyzed using 3×2 repeated-measures ANOVAs with the within-subject factor tDCS (sham, anodal, and cathodal) and attended *hemifield* (left, right). Greenhouse–Geisser correction was applied in case of violation of the sphericity assumption.

EEG RECORDING AND ANALYSIS

During the WM task, EEG was recorded from 19 standard scalp locations according to the European 10–20 system (Fp1, Fp2, F3, F4, F7, F8, Fz, Cz, C3, C4, T3, T4, Pz, P3, P4, T5, T6, O1, O2) using Ag/AgCl electrodes mounted in an elastic cap (Soft Cap EEGH-Z-∗, Walter Graphtec GmbH). The vertical and horizontal electrooculogram was recorded with one electrode placed below and one placed approximately 1 cm to the external canthus of the right eye. EEG data were recorded by a PL-351 amplifier and the corresponding software (Walter Graphtek GmbH) referenced to electrode POz and sampled at 500 Hz. Impedances were kept below 10 kΩ. EEG preprocessing and data analysis were carried out in Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany), and FieldTrip http://fieldtrip.fcdonders.nl/. EEG data were off-line filtered from 1 to 40 Hz and re-referenced to a common average reference. Event-related potentials (ERPs) were segmented into 1300 ms epochs starting 300 ms before the onset of the memory array and covered the retention period, thus analyzing the encoding and retention phase of the WM task. Baseline correction was accomplished between −300 and −200 ms. Segments containing ocular artifacts, movement artifacts, or amplifier saturation were excluded from the averaged ERP waveforms. ERPs for each stimulus (attend left, attend right, separately for sham, anodal, and cathodal) were averaged for each subject and grand-averaged across subjects.

Subsequently, for posterior channels (P3, P4, Pz, O1, O2) peak analysis of the ERP was performed on single-subject averages measured for the ERP components N2 (most negative deflection between 100 and 200 ms), P2 (positive deflection between 180 and 280 ms), and N3 (negative deflection between 240 and 340 ms). Furthermore, the sustained posterior contralateral negativity (SPCN; Klaver et al., 1999) was investigated by calculating the mean amplitude in a latency range between 600 and 700 ms. These latencies were defined on the basis of the grand average computed across all participants and conditions. In the end, amplitude measures were analyzed using separate repeated-measures ANOVAs. These 3×2 ANOVAs included the within-subject factor tDCS (sham, anodal, and cathodal) and attended *hemifield* (left and right). Greenhouse–Geisser correction was applied in case of violation of the sphericity assumption.

Furthermore, event-related spectral perturbations (ERSP) were analyzed for each subject and condition. ERSPs were calculated for parietal and occipital channels (P3, P4, Pz, O1, O2) using a wavelet-based analysis implemented in Brain Vision Analyzer 2.0 software. We used a continuous wavelet transform (WT) with complex Morlet wavelets (Morlet parameter c 3.8; 40 frequency steps from 1 to 40 Hz) to examine the frequency composition of single-trial epochs. The magnitudes of the WTs of single-trial epochs were then averaged to compute the total power of activity, which contains signal components that are phase-locked and non-phase-locked to the stimulus event. For each scale of the WT a baseline correction was applied by subtracting the mean amplitude within the −300 to −50 ms time window from each data point after stimulus onset. tDCS effects on oscillatory brain activity were analyzed by computing ERSP differences between the separate tDCS conditions. For statistical comparisons, we used a non-parametric cluster-based randomization approach built into FieldTrip. All data points (40 frequency steps from 1 to 40 Hz) were included in this global analysis of time frequency bands. In particular, this procedure defined clusters on the basis of the actual distribution of the data and tested the statistical significance of these clusters using a Monte-Carlo randomization method with correction for multiple comparisons (Maris et al., 2007). The clustering used 500 randomizations and was performed in time and frequency simultaneously. The t-statistic of paired t-tests was calculated on a cluster-level by taking the sum of the t-values within the respective cluster (Jacobson et al., 2012).

RESULTS

BEHAVIORAL DATA

The K value (Cowan, 2001), an individual estimate of WM capacity, was calculated for each subject separately for each tDCS condition (cf. **Figure 2**). The 3 × 2 repeated-measures ANOVA with the factors *tDCS* (sham, anodal, cathodal) and *hemifield* (left, right) revealed a significant *tDCS* × *hemifield* interaction [$F(1.8, 20.4) = 4.16$, $P < 0.05$]. Neither the main effect for factor *tDCS* [sham, anodal, cathodal; $F(1.9, 21.6) = 2.12$, $P = 0.15$] nor the main effect for factor *hemifield* [left, right; $F(1.11) = 0.54$; $P = 0.48$] reached statistical significance. Subsequent separate ANOVAs with the factor *tDCS* (sham, anodal, cathodal) for the left and right hemifield revealed a significant main effect of *tDCS* for stimuli attended in the left hemifield only [$F(1.8, 20.6) = 3.93$, $P < 0.05$]. While anodal tDCS of the right parietal cortex decreased WM capacity for contralateral stimuli, cathodal tDCS increased it. For stimuli that had to be attended on the ipsilateral (right) hemifield, both active tDCS conditions interfered with the WM capacity in comparison to the sham condition.

EVENT-RELATED POTENTIALS

Figure 3 illustrates the ERP data for anodal, cathodal, and sham conditions for stimuli attended in the left and right hemifield averaged over 12 subjects for the analyzed electrodes (P3, P4, Pz, O1, O2). Visual stimulation consistently evoked a N2 component at 150 ms which was followed by the P2 component at 230 ms. A N3 component was elicited consistently in all tDCS conditions with a mean latency of 300 ms which was followed by an SPCN component between 600 and 700 ms.

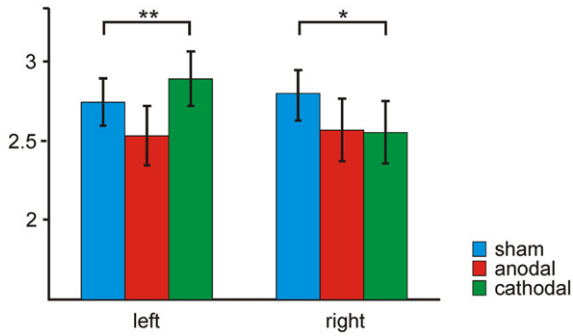

FIGURE 2 | Transcranial direct current stimulation effect on working memory capacity *K*: WM capacity (K) is given for sham (blue), anodal (red), and cathodal (green) tDCS of the right parietal cortex separately for attended stimuli in the left and right hemifield.

For the amplitude of the N2 ERP component the 3 × 2 repeated measurement ANOVAs with the factors *tDCS* (sham, anodal, cathodal) and *hemifield* (left, right) revealed a significant main effect of the factor *tDCS* at electrodes P3 [$F(1.9, 22.2) = 4.64$, $P < 0.05$], and Pz [$F(1.9, 21.4) = 5.29$, $P < 0.05$], and a statistical trend at electrode P4 [$F(1.5, 16.9) = 2.66$, $P = 0.1$]. Anodal tDCS reduced the N2 amplitude as compared to sham and cathodal stimulation regardless of the attended hemifield in the bilateral posterior cortex (cf. **Figure 4**).

Analysis of the amplitude of the P2 component revealed a significant *tDCS* × *hemifield* interaction at electrodes P3 [$F(1.6, 17.2) = 8.82$, $P < 0.01$], and a statistical trend at Pz [$F(1.6, 17.1) = 3.29$, $P = 0.07$]. Subsequent separate ANOVAs with the factor *tDCS* (sham, anodal, cathodal) revealed a significant main effect of the factor *tDCS* for stimuli attended in the right hemifield at electrode P3 [$F(1.8, 20.4) = 5.29$, $P < 0.05$]. Both, anodal and cathodal tDCS decreased the P2 amplitude as compared to sham stimulation for stimuli attended in the right hemifield at left and central posterior electrode sites.

N3 amplitudes were modulated by *tDCS* at electrodes O1 [$F(1.7, 19.2) = 2.69$, $P = 0.09$] and O2 [$F(1.9, 20.9) = 4.69$, $P < 0.05$]. Both, anodal and cathodal tDCS decreased the N3 amplitude as compared to sham stimulation.

Statistical analysis of the SPCN revealed a significant *tDCS* × *hemifield* interaction at electrode P3 [$F(1.8, 19.7) = 5.88$, $P < 0.05$], and a statistical trend at electrode O1 [$F(1.3, 14.2) = 2.68$, $P = 0.09$]. Subsequent separate ANOVAs with the factor *tDCS* revealed significant main effect of the factor *tDCS* for stimuli attended in the left hemifield at electrode P3 [$F(1.4, 15.8) = 4.04$, $P < 0.05$], and for stimuli attended in the right hemifield at electrode O1 [$F(1.5, 17) = 3.48$, $P = 0.06$]. Both, anodal and cathodal tDCS decreased the SPCN amplitude over left posterior scalp regions for stimuli attended in the left hemifield, whereas active tDCS increased the amplitude for stimuli attended in the right hemifield over left occipital scalp regions.

EVENT-RELATED SPECTRAL PERTURBATION

Non-parametric cluster permutation statistics were computed on ERSPs to compare the different *tDCS* conditions. This analysis was

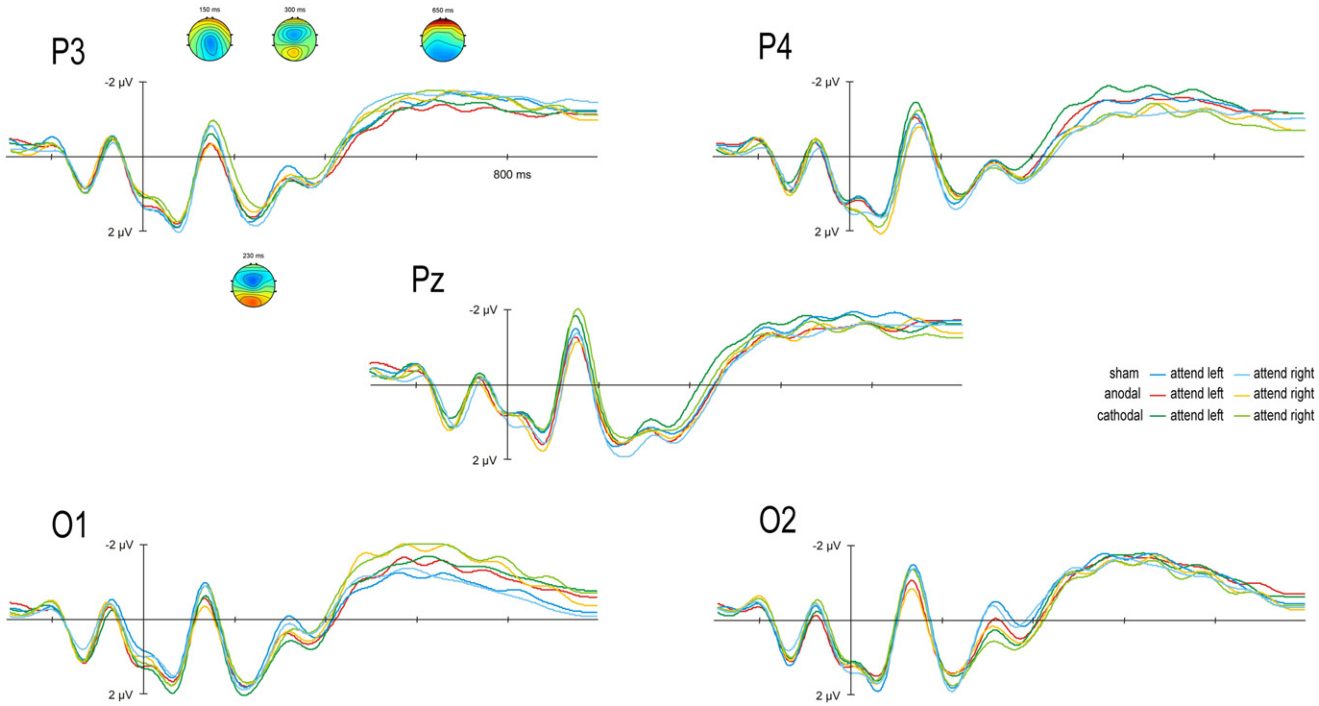

FIGURE 3 | Transcranial direct current stimulation effect on event-related potentials (ERPs): Grand average scalp-recorded ERPs are given for anodal, cathodal, and sham conditions for stimuli attended in the left and right hemifield. ERPs are averaged over 12 subjects for the posterior electrodes P3, P4, Pz, O1, and O2. ERP topographies of grand averages across all conditions are given separately for the N2 (150 ms), P2 (230 ms), N3 (300 ms), and SPCN (1650 ms).

conducted separately for the attend *left* and attend *right* condition and revealed a significant decrease in the alpha band (6–16 Hz), at the latency range of 96–432 ms ($t_{11} \geq 2.2$, $P < 0.05$) after cathodal as compared to anodal tDCS at electrode Pz for the attend right condition only. **Figure 5** shows the ERSP time frequency plots for the sham condition and the active stimulation conditions (anodal, cathodal) plus the corresponding differences at electrode Pz.

DISCUSSION

This study investigated the impact of parietal tDCS on performance in a visuo-spatial WM task and its underlying neural activity. To achieve this goal, participants performed in three separate sessions under sham, anodal, and cathodal tDCS of the right parietal cortex a delayed matching-to-sample task, in which four visual stimuli presented in one visual field had to be memorized and compared with a single subsequently presented test stimulus.

Parietal tDCS during the visuo-spatial WM task had a significant modulatory effect on the WM capacity. Anodal tDCS over the right parietal lobe decreased WM capacity for stimuli attended in the left hemifield, whereas right parietal cathodal tDCS increased WM capacity for attended stimuli in the left hemifield. These modulations in WM capacity can be related to modulated activity in posterior brain areas during the execution of the WM task. Analysis of the ERP during memory encoding and retention revealed that specific ERP components are modulated by the active tDCS conditions. In particular, anodal tDCS generally reduced the N2 amplitude over the bilateral posterior cortex regardless of the attended hemifield, whereas both, anodal, and cathodal tDCS decreased the P2 amplitude for stimuli attended in the right hemifield at left and central posterior electrode sites. Furthermore, active tDCS decreased the N3 amplitude over bilateral occipital areas. The SPCN amplitude over left posterior scalp regions was reduced by active tDCS for stimuli attended in the left hemifield, whereas anodal and cathodal tDCS increased the amplitude for stimuli attended in the right hemifield over left occipital scalp regions. Furthermore, right parietal cathodal tDCS decreased event-related oscillatory power in the alpha band.

On the behavioral level, in the present study we found that cathodal tDCS improved the visuo-spatial WM capacity, whereas anodal tDCS slightly interfered with the WM performance when tDCS was applied over the right parietal cortex. Notwithstanding these results are in contrast to the commonly observed anodal-improvement/cathodal-impairment dichotomy, our tDCS-effects are consistent with recent studies demonstrating tDCS-related modulation of higher cognitive functions. Monti et al. (2008) found that cathodal tDCS over left fronto-temporal areas significantly improved the accuracy of picture naming, whereas anodal tDCS failed to induce any changes. Similarly, You et al. (2011) found that cathodal tDCS over right superior temporal areas induced significantly greater improvements in auditory verbal comprehension than anodal tDCS or sham tDCS over left superior temporal areas. Furthermore, Boggio et al. (2010) found that both, anodal and cathodal tDCS increased the propensity for risk-taking. It has been suggested that the observed improvement after

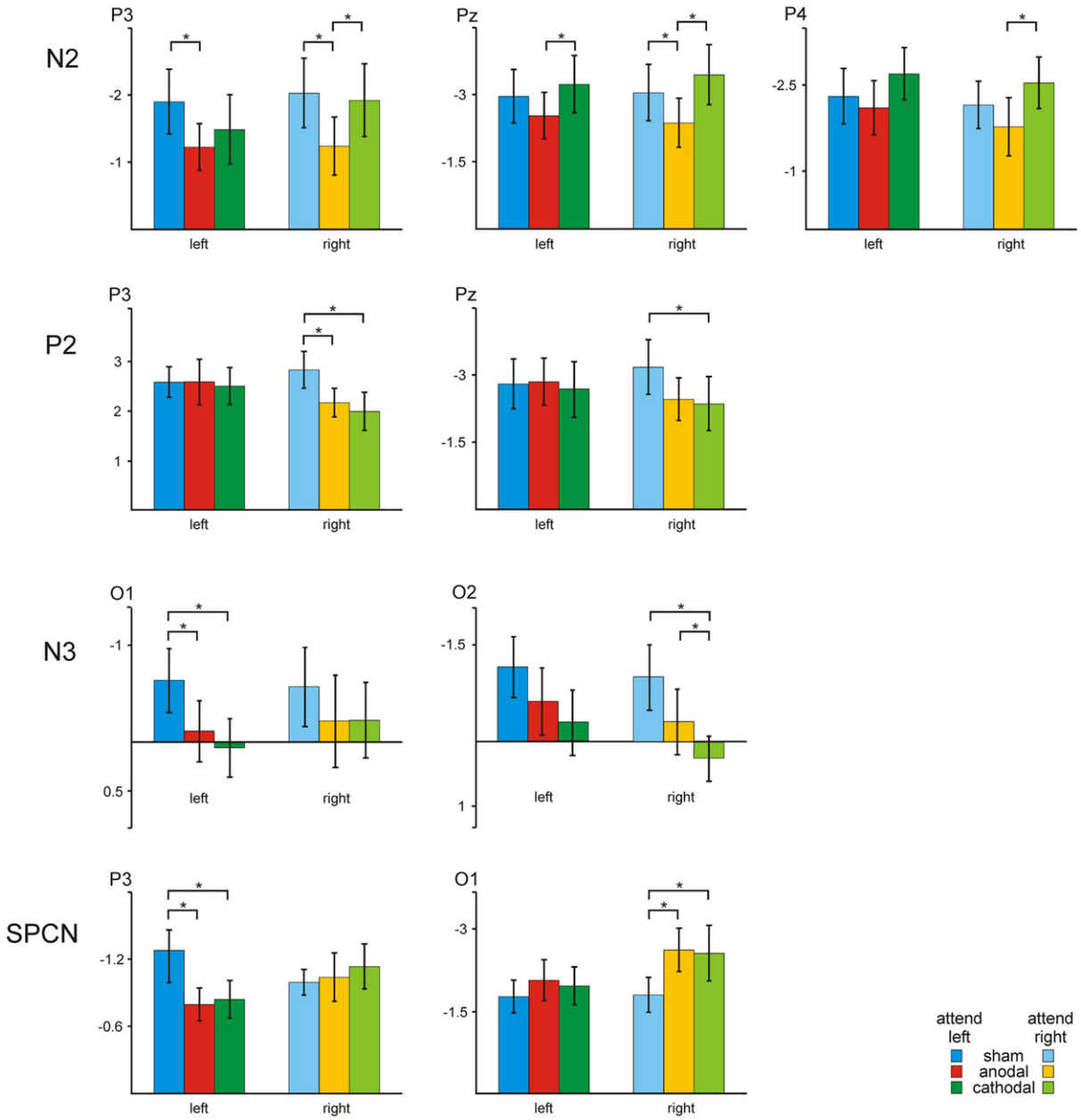

FIGURE 4 | Transcranial direct current stimulation effect on ERP amplitudes: Bar plots show ERP amplitudes at electrodes P3, P4, Pz, O1, and O2 for different conditions (sham, anodal, and cathodal) and the attended hemifield (left, right).

cathodal tDCS might be related to a tDCS-induced depression of cortical inhibitory interneurons, leading to a disinhibition, and, consequently, to an improved functioning of the target cortex (Monti et al., 2008). Generally, the commonly observed anodal-improvement/cathodal-impairment dichotomy is seen mainly in motor studies and rarely in cognitive studies (Jacobson et al., 2012). Furthermore, the distribution of the current flow through the head is much more complex and even common tDCS parameters cannot fully predict the current that reaches the cortex (Neuling et al., 2012). Therefore, in addition to the polarity of modulation, effects of tDCS on WM often depend on additional various factors, such as the task, current density, modulation duration, electrode montage, electrode size, and orientation of the electric field in relation to the anatomical and geometrical feature of the cortex. In the context of the current electrode mounting at parietal electrode sites P7/9, Neuling and colleagues could demonstrate that beside posterior (parietal and occipital) brain areas, also temporal, and frontal cortices reach current densities.

In this study we further assessed the electrophysiological brain activity during the WM task in order to investigate the

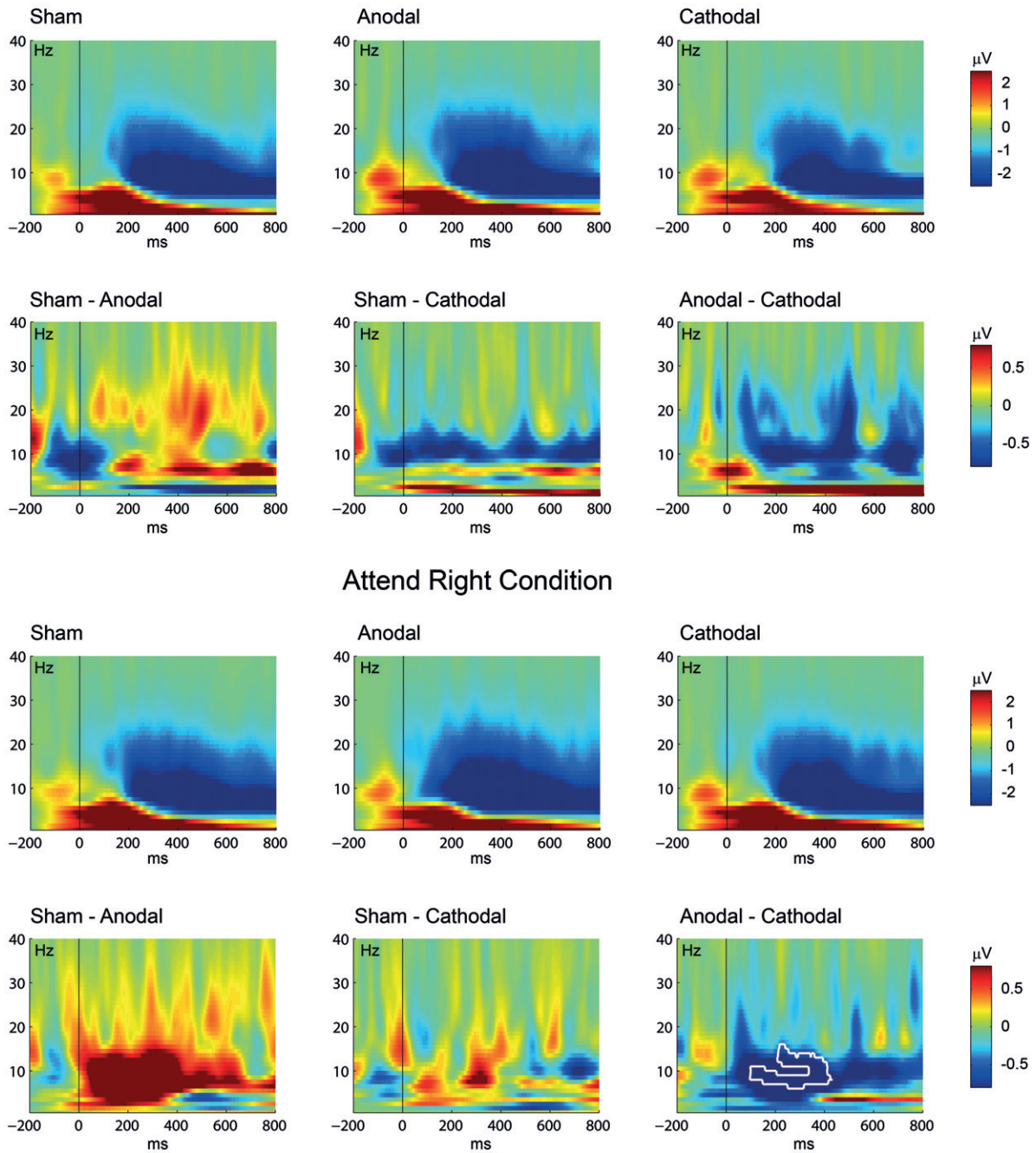

FIGURE 5 | Transcranial direct current stimulation effect on oscillatory brain activity: Event-related spectral perturbation (ERSP) time-frequency plots are given for the sham, anodal, and cathodal conditions. The figure shows the results separately for the attend left (above) and the attend right (below) conditions. Differences between the conditions were computed by subtracting the active ERSPs (anodal, cathodal) from the sham ERSP (left and middle row) or by subtracting the cathodal ERSP from the anodal ERSP (right row). The white contour indicates significant differences between the conditions ($P < 0.05$, corrected for multiple comparisons). Note the different scaling for the ERSP plots (sham, anodal, and cathodal condition; upper rows) and the difference plots (lower rows).

underlying neural mechanisms mediating the tDCS-induced behavioral effects. To date, reports of electrophysiological correlates of tDCS effects are sparse. Using visual ERPs, Antal et al. (2004) demonstrated that the amplitude of the N70 ERP component is increased by anodal tDCS, while it is decreased by cathodal tDCS. The opposite effect has been reported for the visual P100,

showing reduced amplitudes for anodal and increased amplitudes for cathodal stimulation (Accornero et al., 2007). Polarity-specific changes have also been observed for motor cortex excitability (Nitsche and Paulus, 2001) as well as for ERPs in the somatosensory (Matsunaga et al., 2004; Dieckhofer et al., 2006; Antal et al., 2008), and auditory modalities (Zaehle et al., 2011a). In agreement with these findings, our results revealed polarity-specific effects of anodal and cathodal tDCS on cortical activity.

Moreover, during the retention of the visuo-spatial information, we found a significant decrease in oscillatory power in the alpha band for the cathodal tDCS over the parietal cortex. Generally, WM operations have been related to oscillatory brain activity in multiple frequency bands, including the theta (4–8 Hz), alpha (8–12 Hz), and beta (12–30 Hz) range (Klimesch et al., 2005). In particular the performance in visual WM tasks has been specifically associated with alterations in event-related alpha band activity (Pesonen et al., 2007). In this regard alpha activity is assumed to reflect a general inhibition of non-task relevant areas (Klimesch, 1999) and may index the degree of inhibition necessary during internally, as opposed to externally, directed attention (Cooper et al., 2003). Furthermore, alpha activity increases during the retention interval of memory tasks, when participants need to keep in mind several items after encoding, and later responded to a probe (Klimesch, 1999; Busch and Herrmann, 2003; Sauseng et al., 2005; Klimesch et al., 2007). Moreover, alpha power increases with increasing number of items to be remembered (Klimesch, 1999; Jensen et al., 2002; Schack and Klimesch, 2002). Thus our finding of an increase in alpha activity by means of cathodal tDCS might be directly related to the increased performance of the participants in the WM task.

Previously, we showed that tDCS over the left DLPFC induces altered WM performance by modulating its alpha activity. In particular, we demonstrated that cathodal tDCS of the left DLPFC decreases alpha activity over posterior scalp locations (Zaehle et al., 2011b). This effect is in accordance with the present data showing decreased posterior alpha activity after cathodal tDCS of the right parietal lobe. Even though we previously interpreted the modulatory effects of tDCS on WM to be specifically related to the responsiveness of the left DLPFC, it can be assumed that altered local cortical excitability in one part of the responsible network influences the whole neural network associated with WM functions beyond the site of stimulation leading to comparable electrophysiological effects. Thus, the reduction of alpha band activity after cathodal tDCS of either the left DLPFC or the right posterior parietal cortex might be related to general effects of the tDCS on the underlying fronto-parietal network involved in visuo-spatial WM. Indeed, widespread tDCS-induced changes in cortical activity have been demonstrated by a previous neuroimaging study (Keeser et al., 2011). Moreover, it can be demonstrated by simulation approaches, that the mounting of the current electrode at parietal electrode sites P8/P10 induces currents not only to posterior (parietal and occipital) brain areas, but also to the temporal and frontal cortices. Thus, it is likely that by influencing one component of the WM network, the electrical stimulation had an influence on the functioning of the entire WM system.

In the present study we also revealed tDCS-related effects for stimuli attended in the right hemifield, i.e., ipsilateral to the active tDCS stimulation. Even though EEG studies consistently report parietal contralateral activity during visual WM tasks to be strongly lateralized (Klaver et al., 1999; Vogel and Machizawa, 2004), functional magnetic resonance imaging (fMRI) also emphasizes bilateral parietal BOLD activation (Robitaille et al., 2010). It has been proposed that this discrepancy might relate to the different temporal resolutions of both methods. It might be that the mnemonic representations of the parietal cortex are initially lateralized, but become more bilateral over time within one trial. Thus, give the good temporal resolution of EEG data, the lateralized ERP components are more suitable to detect this specific differences and fMRI is not able to resolve this transient effects (Robitaille et al., 2010). However, based on these divergent reports we cannot rule out bilateral involvement of the parietal cortex during the particular paradigm used in the present study. Consequently, the involvements of the ipsilateral hemisphere might explain the observed electrophysiological and behavioral effects on stimuli that have been attended in the right hemifield.

In summary the present study shows that tDCS of the parietal cortex can change the organized cortical activity associated with visuo-spatial WM in concert with systematic alterations of WM performance. To our knowledge, this is the first study investigating the effects of parietal tDCS on electrophysiological brain activity in the context of a visuo-spatial WM task. The results of the study will provide a better understanding of the neuromodulatory effects of tDCS and demonstrate its potential at fostering knowledge for therapeutic application of tDCS in neuropsychiatric diseases.

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Pharmacological modulation of the short-lasting effects of antagonistic direct current-stimulation over the human motor cortex

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Combined administration of transcranial direct current-stimulation (tDCS) with either pergolide (PER) or d-cycloserine (d-CYC) can prolong the excitability-diminishing effects of cathodal, or the excitability enhancing effect of anodal stimulation for up to 24 h poststimulation. However, it remains unclear whether the potentiation of the observed aftereffects is dominated just by the polarity and duration of the stimulation, or the dual application of combined stimulation and drug administration. The present study looks at whether the aftereffects of oral administration of PER (a D1/D2 agonist) or d-CYC (a partial NMDA receptor agonist), in conjunction with the short-duration antagonistic application of tDCS (either 5 min cathodal followed immediately by 5 min anodal or vice versa), that alone only induces short-lasting aftereffects, can modulate cortical excitability in healthy human subjects, as revealed by a single-pulse MEP (motor-evoked-potential) paradigm. Results indicate that the antagonistic application of tDCS induces short-term neuroplastic aftereffects that are dependent upon the order of the application of short-duration stimulation. The administration of d-CYC resulted in a marked inhibition of cortical excitability under the application of tDCS in both stimulation orders. Intake of PER resulted in an increase in cortical excitability in both stimulation orientations, but was non-significant compared to the placebo condition. These results indicate that the aftereffects of tDCS are dependent upon the order of stimulation applied, and also demonstrate the prolongation of tDCS aftereffects when combined with the administration of CNS active drugs.

Keywords: human, tDCS, neuroplasticity, d-cycloserine, pergolide, motor cortex

INTRODUCTION

The effect that transcranial direct current-stimulation (tDCS) exerts on the intact human cortex is closely related to the modulation of cortical excitability and neuronal activity, which are key mechanisms for learning and memory processing (Paulus, 2004). The relevant stimulation parameters encompass the polarity, the current strength, size of the stimulated area, and duration of the stimulation (Nitsche et al., 2008; Stagg and Nitsche, 2011) and are considered to be safe as assessed by several studies (Nitsche et al., 2003b; Iyer et al., 2005; Poreisz et al., 2007). The most common way to evaluate changes in cortical excitability is by applying transcranial magnetic stimulation (TMS) to the motor cortex, since it allows the measurement of reproducible and quantifiable effects through the analysis of motor-evoked-potentials (MEPs). Anodal stimulation increases the amplitude of MEPs while cathodal stimulation decreases them (Nitsche and Paulus, 2000, 2001). The primary effect of tDCS is a neuronal de- or hyperpolarization of the membrane potential (Creutzfeldt et al., 1962; Bindman et al., 1964), whereby the induced aftereffects depend on *N*-methyl-D-aspartate (NMDA) receptor-efficacy changes (Liebetanz et al., 2002). Studies investigating the combined administration of pharmacological agents combined with tDCS, has provided valuable insights into the mechanisms and modes of action that tDCS exerts on neuronal tissue (for a review, see Nitsche, 2005).

The anatomical structure of the cortex means that when using currents to polarize neuronal tissue in the brain, a homogeneous induction of either excitability increase or decrease is prevented by the folded cortex. If for example, current flows through a cortical gyrus, on one side of the gyrus wall an excitability increase is induced, whereas on the opposing side, a excitability diminution cannot be avoided (Creutzfeldt et al., 1962; Lang et al., 2005; Datta et al., 2009). This is a consideration when utilizing tDCS as treatment in neurological disorders, such as epilepsy, as any unwanted excitability increases may theoretically worsen seizure frequency or intensity. The aim of the present study was to find a pharmacological solution for this problem by investigating whether we were able to induce changes in cortical excitability using short-duration antagonistic applications of tDCS in combination with CNS active drugs that have been shown to prolong neuroplasticity-inducing aftereffects.

To investigate this question, we stimulated the motor cortex in two opposing directions during one stimulation application in addition to administering D-cycloserine (D-CYC) a drug

selectively prolonging the excitability enhancement induced by anodal stimulation) or pergolide (PER; a drug selectively prolonging the excitability reduction induced by cathodal stimulation) as well as a placebo (PLC) control. After drug intake, a 5-min anodal followed by a 5-min cathodal (or vice versa) antagonistic stimulation was applied to the primary motor cortex (M1) in a healthy participant population. Previous studies proved that 5 min stimulation duration alone did not evoke aftereffects lasting longer than 5 min (Nitsche and Paulus, 2000). A study by Nitsche et al. (2004a) showed that D-CYC, a partial NMDA agonist, selectively potentiated the duration of motor-cortical excitability enhancements induced by anodal tDCS from approximately 1 h up to 24 h poststimulation without affecting cathodal inhibition. In contrast, PER, a combined D1/D2 receptor agonist, prolonged the excitability-diminishing effects of cathodal tDCS for up to 24 h after stimulation (Nitsche et al., 2006).

D-CYC was initially introduced as a tuberculostatic agent (Walker and Murdoch, 1957) and was later found to be a CNS active drug at very low doses. D-CYC acts at the glycine-binding site of the NMDA receptor, thus facilitating the opening of the NMDA channel (Thomas et al., 1988). In slice preparations, it has been shown that the activation of this subunit is of importance for inducing long-term potentiation (LTP) effects, and that D-CYC can enhance LTP-like neuroplastic effects (Watanabe et al., 1992).

PER, a D1/D2 dopamine receptor agonist, has been shown to have effects on intracortical excitability in the human motor cortex, where it enhanced intracortical inhibition (Ziemann et al., 1996). A more recent study showed that PER consolidated excitability decreases generated by applications of tDCS to the M1, up until the morning after stimulation. Furthermore, co-administration of PER and sulpiride, allowing for D1 activation in the presence of D2 receptor blocking, was not able to re-establish the characteristic alterations in cortical excitability induced by transcranial direct currents. In another study, PER was shown to enhance the effect of tDCS (or in particular cathodal tDCS) in reducing the amplitude of laser-evoked pain potentials applied over the human M1 (Terney et al., 2008). In this study, PER was administered to 12 healthy subjects before tDCS, after assessing subjective acute pain perception induced by a Tm:YAG laser. The amplitudes of the N2 component of the laser-evoked pain potentials, as well as the subjective rating scores, were significantly reduced up to 2 h poststimulation, with PER increasing the efficacy of the effect of the cathodal stimulation for up to 24 h poststimulation. These data strongly argue for the importance of D2 receptor activity for the induction of increases and decreases in prolonged NMDA receptor dependent motor-cortical excitability shifts in humans, as well as a role in the induction of neuroplastic effects in the intact human cortex.

The hypothesis central to this exploratory study was to pursue whether in a paradigm of antagonistic tDCS current flow direction, the choice of either drug shown to potentiate neuroplastic effects in the cortex will finally determine the direction of tDCS aftereffects, either toward an excitation or inhibition of cortical excitability.

MATERIALS AND METHODS

SUBJECTS

Eight healthy subjects participated in each experiment (six male; mean age 25.5). All gave written informed consent. The study was approved by the ethics committee of the University of Göttingen, and conformed to the Declaration of Helsinki.

CURRENT-STIMULATION OF THE MOTOR CORTEX

Direct currents were transferred via a pair of saline-soaked surface sponge electrodes (35 cm^2) fixed to the scalp and delivered by a specially developed battery-driven constant current stimulator (NeuroConn, Ilmenau, Germany). The motor-cortical electrode was placed over the representational field of the right abductor digiti minimi muscle (ADM) as identified by TMS, and the other electrode was located contralateral to the right orbit. In the different experiments, the currents flowed continuously for 10 min (5 min anodal + 5 min cathodal or vice versa) with an intensity of 1.0 mA.

PHARMACOLOGICAL INTERVENTIONS

D-CYC (100 mg), PER (0.025 mg; combined with 10 mg domperidone to avoid nausea) or equivalent placebo (PLC) drugs were administered to the subjects orally 2 h prior to the onset of stimulation. By these means, the *verum* drugs were able to induce a stable plasma level (Deleu et al., 2002) and produce prominent effects in the CNS (Nitsche et al., 2004a, 2006; Kuo et al., 2008). To avoid interference of plasticity induction by cumulative drug effects, each experimental session was separated by at least 1 week. Both the subjects and the investigator conducting the experiment were blinded as to the respective pharmacological and stimulation conditions administered during each experimental session.

MEASUREMENT OF MOTOR-CORTICAL EXCITABILITY

To detect current-driven changes of excitability, motor-evoked potentials (MEPs) of the right ADM were recorded following stimulation of its motor-cortical representational field by single-pulse TMS. These were induced using a Magstim 200 magnetic stimulator (Magstim, Whiteland, Dyfed, UK) and a figure-of-eight magnetic coil (diameter of one winding = 70 mm; peak magnetic field = 2.2 T). The coil was held tangentially to the skull, with the handle pointing backward and laterally at 45° from the midline. The optimal position was defined as the site where stimulation resulted consistently in the largest MEP. Surface EMG was recorded from the right ADM by use of Ag–AgCl electrodes in a belly tendon montage. Raw signals were amplified, band-pass filtered (2–3 kHz; sampling rate, 5 kHz), digitized with a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, UK) controlled by Signal Software (Cambridge Electronic Design, version 2.13), and stored on a personal computer for offline analysis. The intensity of the stimulator output was adjusted for baseline recording so that the average stimulus led to an MEP of ∼1 mV.

EXPERIMENTAL PROCEDURES

The experiments were conducted in a randomized, repeated measurement design. The subjects were seated in a reclining chair. First, the left motor-cortical representational field of the right ADM was identified by use of TMS (coil position that leads to

the largest MEPs of ADM). Then one DC stimulation electrode, to which in the following the terms cathodal or anodal stimulation refer, was fixed at this position, and the other one was fixed at the contralateral forehead above the orbit.

A baseline of TMS-evoked MEPs (60 stimuli) was recorded at 0.25 Hz. Afterward, anodal, cathodal, or sham tDCS was performed for 10 min. After termination of tDCS, 60 MEPs were recorded at 0.25 Hz 0, 5, and then every 10 min up to 60 min poststimulation.

STATISTICAL ANALYSIS

MEP amplitude means were calculated for each time bin covering baseline (60 stimuli) and poststimulation time-points (60 stimuli). These were normalized and are given as ratios of the pre-current baselines.

Separate repeated measurement ANOVAS [independent variables time course, current-stimulation (TYPE: anodal-cathodal or anodal-cathodal), drug condition (PLC vs. D-CYC or PPER), dependent variable MEP amplitude) were calculated for each time bin up to 60 min post-tDCS, for the different stimulation conditions separately. Student's t-tests (paired samples, two-tailed, level of significance <0.05) were performed at each time point to determine whether the MEP amplitudes differed with regard to placebo or the drug administration.

RESULTS

None of the subjects reported any adverse events during and after the experiments.

PLACEBO ADMINISTRATION

The cortical excitability change depended on the application of the second type of stimulation: the anodal-cathodal stimulation resulted in a decrease in cortical excitability while the cathodal-anodal stimulation produced excitation (**Figures 1A,B**). The ANOVA revealed no significant main effect with regard to the TYPE of stimulation [$F(1, 14) = 1.46$, $p = 0.24$] and time course [$F(7, 98) = 0.91$, $p = 0.5$] but the interaction of the TYPE of stimulation × time course showed a tendency [$F(7, 98) = 1.8$; $p = 0.06$]. Student's t-test showed a significant difference at 5′ and 10′ poststimulation between the anodal-cathodal and cathodal-anodal stimulation conditions ($p < 0.05$, $t = 2.54$; 2.4).

CATHODAL-ANODAL CURRENT DIRECTION

After D-CYC administration there was a decrease in cortical excitability using the cathodal-anodal stimulation order (**Figure 1**). Compared to the PLC stimulation, the ANOVA revealed significant main effect of stimulation [$F(1, 14) = 5.97$, $p = 0.03$], but the time course [$F(7, 98) = 0.86$, $p = 0.53$] and the interaction of stimulation × time course [$F(7, 98) = 0.89$, $p = 0.51$] were not significant. The Student t-test showed a significant excitability decrease at 10, and 20 min poststimulation compared to placebo intake ($p < 0.05$, $t = 3.13$; 2.46).

After PER administration there was no detectable after-effect when the cathodal-anodal stimulation combination was applied. Generally, the MEP amplitudes were more unstable compared to the other stimulation condition. Compared to the PLC administration, the ANOVA revealed no main effect of stimulation [$F(1, 14) = 1.98$, $p = 0.16$] and time course [$F(7, 98) = 1.02$, $p = 0.41$] and no significant interaction of stimulation × time course [$F(7, 98) = 1.14$, $p = 0.32$].

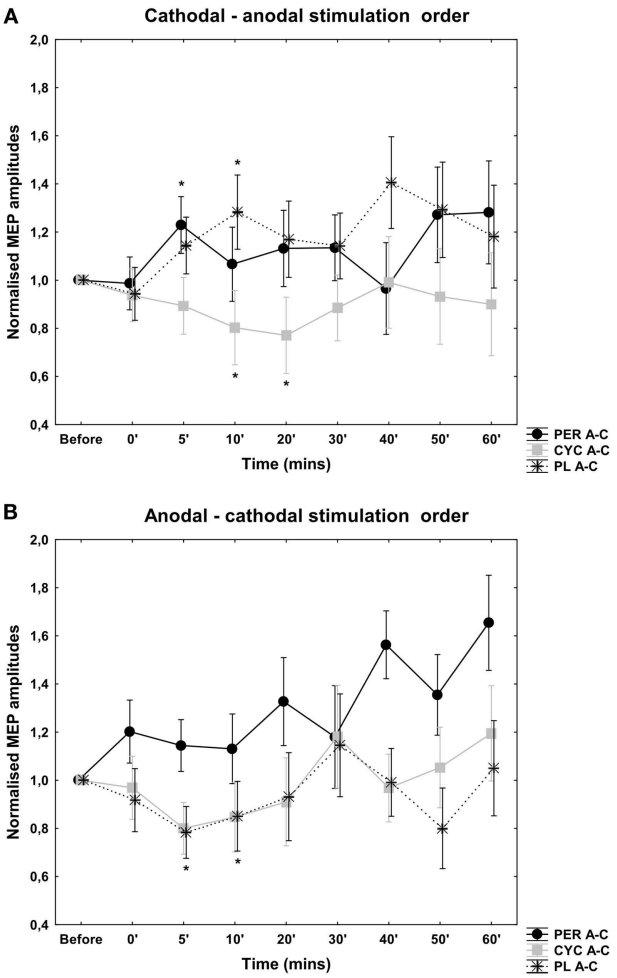

FIGURE 1 | Effects of antagonistic cathodal-anodal (A) and anodal-cathodal (B) tDCS in conjunction with PER, CYC, and PLC control. MEP amplitudes are given as mV, vertical bars indicate SEM. With regard to the PLC condition the order of each short-duration antagonistic tDCS application is the predominating factor in modulating short-duration tDCS aftereffects. A tendency toward excitability enhancement was seen after PER administration in the cathodal-anodal stimulation order. After anodal-cathodal tDCS an increase in cortical excitability is also evident, but was not significant. d-CYC administration resulted in a decrease in cortical excitability regardless of the orientation of stimulation.

ANODAL-CATHODAL CURRENT DIRECTION

However, after D-CYC administration there was no significant change in cortical excitability using the anodal-cathodal stimulation order. There was no significant main effect of stimulation [$F(1, 14) = 0.19$, $p = 0.66$] and time course [$F(7, 98) = 1.54$, $p = 0.16$]. The interaction between the type of stimulation and time course was not significant [$F(7, 98) = 0.43$, $p = 0.8$; **Figure 1**].

Similarly, after PER administration there was no significant aftereffect when the anodal-cathodal stimulation combination was

applied. Generally, the MEP amplitudes were more unstable compared to the other stimulation condition. Compared to the PLC administration, the ANOVA revealed no main effect of stimulation [$F(1, 14) = 0.19$, $p = 0.82$] and time course [$F(7, 98) = 1.43$, $p = 0.19$] and no significant interaction of stimulation × time course [$F(7, 98) = 0.67$, $p = 0.79$].

DISCUSSION

This investigation into the antagonistic application of tDCS revealed that the order of each tDCS primarily determines the induced aftereffects; which was either an increase or decrease in cortical excitability. Initially our hypothesis was to examine whether the administration of a pharmacological agent known to modulate neuroplastic effects in the cortex, would influence the direction of induced aftereffects and/or prolong any measureable aftereffects. We observed that there was no excitatory aftereffect after D-CYC administration for both the cathodal-anodal and anodal-cathodal stimulation orders (only an inhibition was observed), and no inhibitory after-effect after PER administration, irrespective of the current flow direction sequence. A prolongation of tDCS aftereffects outlasting the stimulation duration of 5 min in each polarity (anodal or cathodal tDCS) was observed. In a previous study, Nitsche and Paulus (2000) demonstrated that short-duration tDCS (5 and 7 min) did not produce aftereffects lasting longer than between 5 and 30 min (depending upon the stimulation duration), whereas the present study reports that 10 min of antagonistic tDCS produces at least a 10-min aftereffect post-drug administration. In addition, we observed that the order of stimulation was the dominant modulator of the tDCS-induced aftereffect. For example, when 5 min cathodal-anodal stimulation was applied over the M1, a net excitatory effect was observed, and vice versa for the reverse stimulation combinations for the PLC condition. For the cathodal-anodal stimulation order, there was a net decrease in cortical excitability under D-CYC which showed a significant interaction between the order of stimulation across the measured timecourse (at 5 and 10 min) poststimulation. The administration of PER showed an overall increase in MEP amplitudes but was not significant compared to the PLC condition. In the anodal-cathodal stimulation order, D-CYC and the PLC showed a decrease in cortical excitability over time but this tendency was not significant. PER increased MEP amplitudes compared to the PLC condition, but this was also not significant. The MEPs recorded under PER administration in both stimulation orders were largely unstable and so a significant net increase or decrease in the levels of cortical excitability was difficult to determine. The mechanism of tDCS action has been investigated in many previous human and animal studies (Bindman et al., 1964; Nitsche, 2005; Nitsche et al., 2005) and has also been well characterized by the use of CNS active drugs (Nitsche, 2005). During tDCS, the effects of both anodal and cathodal stimulation are dependent upon fluctuations in membrane potential. However, the induction of tDCS aftereffects can also depend upon synaptic modulation and affect intracortical neurons (as anodal and cathodal DC currents do not influence motor threshold values; Nitsche et al., 2005). The aftereffects of anodal and cathodal tDCS are influenced by the potentiation of receptors at the glutamatergic synapse (Nitsche et al., 2003a), and studies have also shown that they are modulated by dopamine, acetylcholine, and serotonin receptors (Kuo et al., 2007; Monte-Silva et al., 2009; Nitsche et al., 2009). Anodal tDCS is also strongly influenced by GABAergic neurotransmission via the activity of interneurons (Nitsche et al., 2004b). The relatively weak effects of antagonistic tDCS that we have observed in this study may arise for a number of different reasons; the balance between the potentiation of D1 and D2 receptors by PER and the low dosage administered may account for the unstable trend toward cortical excitation. Sampling a larger subject group could also have reduced the high variability in the MEP data and also have made this trend significant. Secondly, the effects of tDCS alone showed that the order of each stimulation application influenced that outcome of the aftereffects. As tDCS is duration dependent, it is also possible that the stimulation duration was not long enough to induce enduring aftereffects. The interaction between PER, D-CYC, and tDCS at the membrane would also have affected the stability of the aftereffects, as tDCS-induced neuroplasticity is NMDA receptor dependent (Liebetanz et al., 2002) and influenced by the ratio of D1/D2 receptors; the potentiation of NMDA receptors may not have been strong enough to overcome the effects of the short-lasting DC modulations. In summary, tDCS aftereffects are dependent upon the polarity of stimulation, duration, and intensity, but are also heavily influenced by neuromodulators potentiating receptors that are present upon the neuronal membrane. Therefore, it is difficult point out a single mode of action that is responsible for the aftereffects observed here.

The effects of antagonistic tDCS have not been widely investigated until now. Priori et al. (1998), whilst looking at DC polarization of the motor cortex, reported that pulses of anodal DC only changed the amplitude of elicited MEPs when there was an alternation in the application of anodal and cathodal DC. Based upon animal data (Stafstrom et al., 1984), they suggested that there may be a degree of neuronal adaptation, whereby neuronal elements compensate for the DC-induced changes in the membrane potential. This indicated that by alternating the anodal-cathodal DC sequence, the targeted neuronal elements were prevented from adapting to the polarizing DC stimulation.

We were able to observe a significant inhibition in cortical excitability when tDCS in the cathodal-anodal current direction was applied under D-CYC administration. These results are similar to the data published by Kuo et al. (2008). The combined application of cathodal-anodal tDCS and D-CYC within independent experimental sessions, were examined in conjunction with mechanisms of homeostatic plasticity during a motor learning task. The excitability diminution induced by cathodal tDCS prior to motor learning, or an excitability enhancement induced by anodal tDCS if combined with the partial NMDA receptor agonist D-CYC, impaired learning performance. Similarly to these data, we have observed a decrease in MEP amplitude, when the cathodal-anodal stimulation condition was applied. However, the stimulation duration was shorter compared to those applied in previous studies with D-CYC, which may account for the differences reported in this study.

In our study, the oral administration of PER did not induce any significant aftereffect poststimulation, and the results were not significantly different from those obtained under the PLC condition

although a tendency toward excitability enhancement could be seen. This was possibly due to the increased variability of MEP amplitudes after PER intake. We have seen that administration of PER increased the instability of MEPs (and thus the variability of MEP amplitudes) after the antagonistic administration of tDCS. The possible cause of this instability could be attributed to the very low dose of PER given in this study, compared to those of other studies reporting the effects of PER on transcranial stimulation measured using TMS-elicited MEPs (Lang et al., 2008). As previously mentioned, the variability may also have been decreased by increasing the number of participants that were involved in the study.

Dopaminergic (DA) mechanisms have been demonstrated to stabilize these processes involved in neuroplasticity induction (for a review examining the effects of dopamine on cortical excitability, see Nitsche et al., 2010). DA acting on D1 receptors increases NMDA currents (Cepeda and Levine, 1998). In addition, the enhancement of D2 – and to a lesser degree – of D1 receptors by pergolide consolidated tDCS generated excitability diminution up until the morning post stimulation (Nitsche et al., 2006). A number of recent studies have looked at the interaction of the dopaminergic system with tDCS applied to the cortex. One study examining the dose-dependent effects of dopamine on plasticity processes employed two varying methods to either induce focal (paired-associative stimulation, PAS) or non-focal (tDCS paradigms) plasticity in the motor cortex. The authors demonstrated that administration of varying dosages of ropinirole, a D2/D3 dopamine agonist, resulted in an inverted "U"-shaped dose-response curve on excitability enhancing tDCS and PAS protocols, as well as inhibitory tDCS protocols. They concluded that in high or low dosages, ropinirole attenuated plasticity-inducing processes, and that neuroplasticity processes involving D2 receptor potentiation are subject to dose-dependent effects, and can be considered when examining inhibitory and facilitatory mechanisms of plasticity, depending upon the type of plasticity induced (Monte-Silva et al., 2009). A similar study showed that L-dopa administered in high (200 mg) or low (25 mg) doses abolished facilitatory and inhibitory cortical plasticity, whereas a medium dose (100 mg) reversed facilitation into inhibition in the motor cortex, as well as prolonging inhibitory plasticity (Monte-Silva et al., 2010). Investigations into the impact of dopamine on learning and memory formation demonstrate that dopamine also has a focusing effect on neuroplasticity processes. A study looking at the influence of D1 receptors showed that the balance between D1 and D2 receptor activity is crucial in both the consolidation of resultant excitability changes arising from non-focal (tDCS) and focal (PAS; in this case inhibitory, iPAS, or excitatory, ePAS), neuroplasticity-inducing paradigms, and to generate a focusing effect of plasticity (Nitsche et al., 2009). The possible mechanisms of DC-induced aftereffects were investigated in several previous studies; pharmacological intervention suggests that the aftereffect is *N*-methyl-D-aspartate (NMDA)-receptor dependent (Liebetanz et al., 2002; Nitsche et al., 2004a,b,c). NMDA receptor and intracellular sigma 1 receptor blocker dextromethorphan intake prevented both anodal and cathodal tDCS-induced aftereffects, demonstrating that dextromethorphan critically interferes with the functionality of tDCS irrespective of the polarity of the DC stimulation. It is known that long-lasting NMDA receptor dependent cortical excitability and activity shifts are involved in neuroplastic modification. Another study revealed that NMDA receptor antagonist dextromethorphan did not changes levels of cortical excitability during a short-duration of tDCS, and also prevented any enduring aftereffects of tDCS, independent of stimulation polarity (Nitsche et al., 2003a).

Homeostatic mechanisms are might also play a role in the observable aftereffects of tDCS, a state whereby neurons in the nervous system dynamically adjust synaptic strengths favoring the direction that promotes stability in growing networks. This process is not unlike Hebbian mechanisms of plasticity, but differs fundamentally in the sense that Hebbian mechanisms tend to destabilize neural circuits and homeostatic mechanisms can relate complex neural networks responsible for processes ranging from memory storage to activity dependent development, and so by their very nature are more stable (Turrigiano and Nelson, 2000, 2004). Preconditioning the M1 with tDCS can shape the magnitude and direction of excitability changes induced by a subsequent session of repetitive TMS (rTMS). Lang et al. (2004) published a study demonstrating that anodal tDCS causes a subsequent application of 1 Hz rTMS to reduce corticospinal excitability, while preconditioning with cathodal tDCS induces the reverse effect. However, our present data are not in agreement with these previous results, suggesting that for the manifestation of homeostatic mechanisms longer stimulation durations may be required, or that this kind of plasticity has a limited influence when more components (drug application and antagonistic external stimulation) are administered at the same time.

In this exploratory investigation, we are able to reveal that stimulation duration has a much greater impact on modulating cortical excitability than the administration of sub-therapeutic levels of CNS active drugs, in combination with tDCS. Further experimental work would need to be conducted in order to understand whether it was initially the use of a shorter stimulation duration in this antagonistic stimulation sequence, or the antagonistic administration of tDCS in combination with PER or D-CYC that may have resulted in the aftereffects that we report here; this may be the critical limiting step within the paradigm that we have chosen to implement in this study. Previous studies have highlighted the efficacy of non-invasive brain stimulation devices used in combination both with and without CNS drugs in the treatment of neurological disorders, for example in the treatment of chronic pain (Antal and Paulus, 2011), migraine (Antal et al., 2011), and depression (Loo et al., 2012). With this study we aimed to investigate whether the antagonistic application of tDCS in combination with PER and D-CYC could induce changes in cortical excitability, and modulate these excitability changes long enough to provide an insight into whether short-duration tDCS could be used as a therapeutic approach for neurological disturbances.

CONCLUSION

The present study reports that administration of CNS active drugs in combination with short-duration tDCS can modulate tDCS-induced aftereffects in the healthy human motor cortex. The predominant factor influencing the outcome of these effects is the order of antagonistic short-duration tDCS application.

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Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans

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The prefrontal cortex is involved in mood and emotional processing. In patients suffering from depression, the left dorsolateral prefrontal cortex (DLPFC) is hypoactive, while activity of the right DLPFC is enhanced. Counterbalancing these pathological excitability alterations by repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) improves mood in these patients. In healthy subjects, however, rTMS of the same areas has no major effect, and the effects of tDCS are mixed. We aimed to evaluate the effects of prefrontal tDCS on emotion and emotion-related cognitive processing in healthy humans. In a first study, we administered excitability-enhancing anodal, excitability-diminishing cathodal, and placebo tDCS to the left DLPFC, combined with antagonistic stimulation of the right frontopolar cortex, and tested acute emotional changes by an adjective checklist. Subjective emotions were not influenced by tDCS. Emotional face identification, however, which was explored in a second experiment, was subtly improved by a tDCS-driven excitability modulation of the prefrontal cortex, markedly by anodal tDCS of the left DLPFC for positive emotional content. We conclude that tDCS of the prefrontal cortex improves emotion processing in healthy subjects, but does not influence subjective emotional state.

Keywords: emotion, prefrontal cortex, face recognition, brain, human

INTRODUCTION

The prefrontal cortex takes part in the neuronal networks involved in mood and emotion processing. Hereby emotion can be defined as a relatively brief, reactive, and intensive emotional state, whereas mood is a more stable, constant, and less reactive emotional state (Ekman, 1999; Ellis and Moore, 1999). In healthy subjects, the ventromedial, and inferior-medial prefrontal cortex are prominently involved in self-referenced affective state (Phan et al., 2002; Steele and Lawrie, 2004). The dorsolateral prefrontal cortex (DLPFC) is more involved in processing of stimuli with not self-referential emotional content, e.g., faces or visual scenes (Ueda et al., 2003; Sergerie et al., 2005; Grimm et al., 2006). However, this distinction, which reflects the fact that the medial prefrontal cortex is generally more heavily involved in emotional, and the lateral prefrontal cortex in cognitive processing, is gradual (Steele and Lawrie, 2004). Moreover, a hemispherical difference of processing of positive and negative emotional content has been described. Happy mood and positive emotional stimuli induce predominant left DPLFC activity (Habel et al., 2005; Herrington et al., 2005; Sergerie et al., 2005). In accordance, lesions of the left prefrontal cortex by stroke, tumors, or epilepsy are often accompanied by depression, while lesions of the right prefrontal cortex are associated with elated mood (Robinson and Lipsey, 1985; Perini, 1986; Belyi, 1987). Clinical depression is associated with left DLPFC hypoactivity, while activity of the right prefrontal cortex might be increased (Schutter and van Honk, 2005).

Consequently, it has been proposed that an activation of the left DLPFC might turn mood and emotion into more positive states. Indeed, activity-enhancing repetitive transcranial magnetic stimulation (rTMS) improves symptoms of depressed patients (Mitchell and Loo, 2006). A similar result was found for excitability-enhancing transcranial direct current stimulation (tDCS; Fregni et al., 2006). Moreover, excitability-enhancing tDCS improved performance in an affective go-non-nongo task for positive emotional content in depressed subjects (Boggio et al., 2007). tDCS induces long-lasting, stimulation polarity-dependent excitability shifts of the human cerebral cortex via neuronal de- or hyperpolarization and the subsequent modification of NMDA receptor strength (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003a,b).

Enhancing excitability of the left DLPFC in healthy humans by rTMS so far failed to induce a positive shift of emotional state (Mosimann et al., 2000; Baeken et al., 2006). However left prefrontal rTMS was able to modulate mood-related information processing (Schutter and van Honk, 2006). Studies exploring alterations of emotional state by prefrontal tDCS in healthy subjects show mixed results. Plazier et al. (in press) describe no effects of prefrontal tDCS on subjective mood. However, the emotional valence of unpleasant pictures was diminished via left DLPFC anodal tDCS (Boggio et al., 2009; Maeoka et al., 2012).

In the present study, we aimed to disentangle the effect of prefrontal tDCS on subjective emotional state and emotional state-related information processing in healthy humans. In the first experiment, we tested the effect of excitability-enhancing anodal

tDCS, excitability-diminishing cathodal tDCS, or sham tDCS of the left DLPFC (combined with antagonistic stimulation of the right frontopolar cortex) on self-referenced emotional state via a visual analog scale (VAS). If tDCS works similarly in healthy subjects and depressed patients, anodal tDCS should shift emotional state to more positive values. In the second experiment, we tested the effect of the identical tDCS protocols on not self-referenced emotional state-related information processing. DLPFC function might be involved more in the latter kind of tasks than in actual modulation of emotional state in healthy subjects. Moreover, the left DLPFC is important for the processing of positive affects. Thus we hypothesized a positive effect of excitability-enhancing tDCS for emotionally positive material. Since the main aim of this study was to explore the effects of a tDCS protocol used for the treatment of depression on emotional state and emotional processing in healthy individuals, we performed only left DLPFC anodal stimulation, and did not explore the effects of right DLPFC anodal tDCS, which might result in antagonistic effects.

MATERIALS AND METHODS

SUBJECTS

Fourteen healthy volunteers (five female, mean age 33.29 ± 8.49 SD) participated in Experiment 1. Seventeen subjects participated in Experiment 2 (eight female, mean age 24.88 ± 2.34 SD). All gave written informed consent. The investigation was approved by the ethics committee of the University of Goettingen, and the experiments conform to the principles laid down in the Declaration of Helsinki.

tDCS OF THE DLPFC

Current (1 mA) was induced through saline-soaked sponge electrodes (surface 35 cm^2), resulting in a current density of 0.0286 mA/cm^2. tDCS was delivered by a specially developed, battery-driven constant-current stimulator (Schneider Electronic, Gleichen, Germany). Current strength was ramped up in the first 10 s of tDCS and turned off the same way to avoid phosphene perception and diminish tingling sensations. For placebo tDCS, current flow was terminated after 20 s. These stimulation characteristics reliably allow placebo stimulation, i.e., subjects are not able to discriminate real from sham stimulation (Gandiga et al., 2006). In Experiment 1, real tDCS was delivered for 20 min, in Experiment 2 for 10 min. Former experiments have shown that these stimulation durations induce cortical excitability shifts stable for at least 1 h after the end of tDCS (Nitsche and Paulus, 2001; Nitsche et al., 2003a). We applied 20 min stimulation in Experiment 1, because this is the usual stimulation duration performed for the treatment of depression (Fregni et al., 2006). tDCS duration in Experiment 2 was 10 min, because this was the duration of the face recognition task, during which tDCS was performed. The left DLPFC electrode (to which the terms anodal and cathodal stimulation refer to) was placed at F3 (international 10–20 system) and the return electrode above the contralateral orbit in both experiments.

QUESTIONNAIRES

For evaluation of emotional state, a questionnaire (Skala zur Einschätzung der Stimmung, SES; Hampel, 1977) was used. The SES is a VAS in German language, which contains adjectives representing happy and sad emotional state as well as lethargy (neutral mood condition). Fourteen adjectives per category were included. The VAS scale ranges from 1 (absent) to 7 (maximum strength). In difference to the more widely used PANAS (Watson and Clark, 1988), which was developed to obtain dispositional affect measures over the last 12 months for positive and negative mood, the SES specifically measures actually present emotion, and adds another emotional dimension, i.e., the neutral emotion condition. Moreover, the VAS of the SES contains seven stages, that of the PNAS only five. We chose the SES instead of the more widely used PANAS, because it is explicitly validated for present emotional state. A limitation of this choice might be the limited comparability with other studies, in which the PANAS was applied. For assessment of depression, subjects performed the Beck Depression Inventory (BDI), and the Hamilton Depression rating scale (HAMD). The BDI is a 21-item self-assessment test presented in multiple-choice format, which measures the presence and the degree of depression in adults (Beck et al., 1961). The HAMD is a 21-item peer-evaluation test, which rates the presence of depressive symptoms as established in a clinical interview (Hamilton, 1960).

EMOTIONAL FACE RECOGNITION TASK

In this task, two emotional expressions of a human face are simultaneously presented on a computer monitor, one joy, or anger, and the other neutral.

Subjects were instructed to identify as fast as possible the position of the emotionally positive or negative facial expression and to press the appropriate button on a keyboard.

All stimuli used in the study were part of Ekman's series of pictures of facial affect (Ekman and Friesen, 1975, 1976). They were presented by a DOS-based software for creating, conducting, and analyzing reaction time tasks (Experimental Run Time System©, BeriSoft Cooperation) on a IBM-compatible computer connected with a 21″ monitor.

Every trial consisted of the simultaneous presentation of two pictures on the left and right side of the screen for 50 ms. The two pictures showed the same person, on one side with an emotional expression (positive, i.e., joy, or negative, i.e., anger) as the target stimulus, on the other side with a neutral facial expression. The two pictures were followed by two question marks presented in place of the facial affect stimuli. Subjects were instructed to judge on which side of the screen the face with an emotional expression had been shown by pressing the left or right button on the keyboard. A red colored cross was shown for 1000 ms to mark the beginning of a trial and to make the subject fixate the center of the screen. **Figure 1** shows an example of the trial structure.

Twelve different trial conditions emerged from randomly varying the position of the target stimulus (left; right), the emotional value of the target stimulus (positive; negative), and the identity of the person on the pictures (female; male no. 1; male no. 2). Each trial condition was shown for four times within a session. Each session consisted of 50 trials, with two randomly chosen warm-up trials not being included in the statistical analysis and 48 permutated experimental trials.

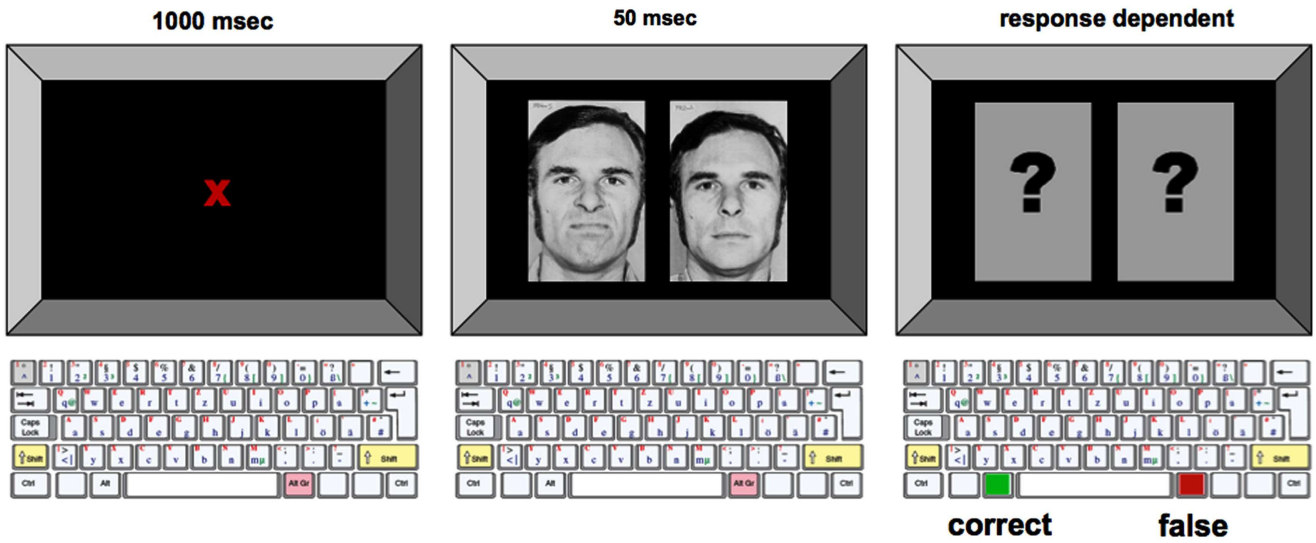

FIGURE 1 | Experimental procedure for the emotional face identification task. Example of the trial with male no. 2, and the target stimulus showing the negative facial expression presented on the left side of the screen. In each trial, emotionally neutral and negative/positive facial expression were displayed simultaneously on the computer monitor. To avoid the development of perceptual strategies, subjects were instructed to focus on a dot placed in the middle of the screen during the whole course of the experiment. Subjects were instructed to press the appropriate button on a keyboard as fast as possible once the visual stimuli were displayed.

EXPERIMENTAL PROCEDURES

Experiment 1

To exclude a state of clinical depression in our healthy subjects, HAMD and BDI were performed before the start of each experimental session.

Afterward, subjects evaluated emotional state before and repetitively after anodal, cathodal, or placebo tDCS. The order of application of the tDCS session was randomized. A complete crossover design was performed. Between each tDCS session, a break of at least 1 week was obligatory to avoid interference effects of stimulation.

Subjects were seated in front of a table, and the position of F3 was identified according to the international 10–20 system. Afterward, the SES was handed out. Subjects were specifically instructed to evaluate their actual emotional state. After baseline measures, the tDCS electrodes were fixed onto the head and tDCS was performed for 20 min with 1 mA current strength. Immediately after the end of tDCS subjects performed the SES again. SES-based evaluation of emotional state was repeated every 15 min for up to 1 h after the end of tDCS and each hour after tDCS for the next 5 h. A last emotional state evaluation was performed the morning after stimulation.

Experiment 2

In this experiment, subjects had to identify the position of the "emotional" facial expression on a computer screen as fast as possible before and repetitively after anodal, cathodal, or placebo tDCS. The order of application of the tDCS sessions was randomized. A complete crossover design was performed. Between each tDCS session, a break of 1 week was obligatory to avoid interference effects of stimulation.

Subjects were seated in front of the screen (eye-screen distance about 75 cm, visual angle approximately 60° in width and height), the position of the tDCS electrodes was identified and the electrodes fixed onto the head. They were instructed that they should identify the position of the emotionally not neutral face out of two simultaneously displayed faces on the computer screen as fast as possible while fixating a dot positioned in the middle of the screen and press the appropriate button on the keyboard as fast as possible. Afterward, all faces were presented once and a short trial run was performed to ensure that the subjects had understood the task. Before tDCS, one baseline session was performed. Then tDCS was started and continued for 10 min. During tDCS, two face recognition sessions were performed, one 2 min after the start of tDCS, the other after 6 min. The remaining face recognition sessions were performed immediately after the end, and 5, 10, 20, 30, and 60 min after the end of tDCS.

CALCULATIONS AND STATISTICS

Experiment 1

For the SES, the sum of the VAS values for each emotional condition (neutral, positive, negative) was calculated intraindividually for each time point/tDCS condition combination. To rule out a systematic influence of subtle baseline differences on the results, the post-tDCS values were standardized by calculating the quotient of post-tDCS values vs baseline measures. Repeated measure ANOVAs were calculated for the absolute and standardized values (repeated measure factors tDCS, emotion, time course, dependent variable VAS score). In case of significant results in the ANOVA, *post hoc* Student's *t*-tests (repeated measures, two-tailed) were calculated to identify significant mood differences for each time point vs baseline for each tDCS condition, and differences between tDCS conditions (anodal/cathodal vs sham stimulation) for each

time point. Critical level of significance was set to 0.05 for all calculations. The *post hoc* tests were not corrected for multiple comparisons.

Experiment 2

Individual means of reaction times were calculated for positive and negative affective face recognition for each tDCS condition and time point separately. Only correct trials were included in the calculations. To exclude a systematic influence of subtle baseline differences on the results, the post-tDCS values were standardized by calculating the quotient of during- and post-tDCS values vs baseline measures. Data were pooled for the two measures during tDCS, measures immediately and 5 min after tDCS, 10 and 20 min after tDCS and 30 and 60 min after tDCS. Repeated measure ANOVAs were calculated for the standardized values (repeated measure factors tDCS, emotion, time course, dependent variable reaction time). In case of significant results of the ANOVA, *post hoc* Student's *t*-tests (repeated measures, two-tailed) were added to identify significant mood differences for each time point dependent on tDCS condition, and to compare baseline performance. The critical *p*-value was set to 0.05 for all calculations. The *post hoc* tests were not corrected for multiple comparisons.

The same calculations were performed for the count of correct answers.

RESULTS

EXPERIMENT 1

For the healthy subjects, the mean BDI values were between 0.79 and 1.5 and the range of the mean HAMD values was 0.93–1.07 for all stimulation conditions. These were identical between the respective tDCS conditions according to the results of the *t*-tests ($p > 0.05$).

Skala zur Einschätzung der Stimmung

For the healthy subjects, the ANOVA (absolute values) revealed significant effects of emotion and the interaction of tDCS × time, but the interactions tDCS × emotion and time × tDCS × emotion, which would have revealed an impact of tDCS on emotional state, were not significant. For the standardized values, however, additionally the main effect for time and the interactions time × emotion, time × tDCS, and time × emotion × tDCS were significant (**Table 1**). Comparing effects of anodal and cathodal tDCS with placebo stimulation for each time point after tDCS separately however did not reveal significant effects of tDCS on neutral, positive, or negative emotional state. As can be seen from **Figure 2**, in all stimulation conditions the healthy subjects rated neutral and negative mood items near the minimum, while positive adjectives were rated generally on a much higher level throughout the experiment.

Baseline values of each emotional quality did not differ significantly between tDCS sessions.

EXPERIMENT 2

Reaction times

The ANOVA revealed a significant main effect of time (**Table 1**). An additional trend for an effect of tDCS on performance was identified. As depicted in **Figure 3**, reaction times diminished throughout the course of the experiment in all tDCS and facial expression conditions. We conducted exploratory, subjected to confirmation, *post hoc t*-tests despite only trend wise effects of tDCS or the interactions including tDCS in the ANOVA. These revealed significant shortenings of reaction time relative to baseline during and after anodal tDCS for positive and negative emotional expressions. For cathodal tDCS, the direction of the improvements of reaction time were similar, but somewhat smaller as compared to anodal tDCS for positive emotional expressions. Conversely, under placebo stimulation the reaction time improvements occurred later during the course of the experiment and were significant – as compared to baseline – only for the last measures. The *post hoc* tests additionally revealed significant reaction time differences for anodal tDCS vs

Table 1 | Results of the ANOVAs conducted for the SES and emotional face identification task.

Variables	d.f.	$d.f._{error}$	*F*-value	*p*	η^2
EXPERIMENT 1					
SES, absolute values					
tDCS	2	26	2.148	0.137	0.142
Emotion	2	26	218.943	<0.001*	0.944
Time	11	143	0.924	0.519	0.066
tDCS × emotion	2	52	0.953	0.441	0.068
tDCS × time	22	286	1.862	0.012*	0.125
Emotion × time	22	286	1.305	0.166	0.091
tDCS × emotion × time	44	572	1.277	0.114	0.089
SES, standardized values					
tDCS	2	26	2.431	0.108	0.158
Emotion	2	26	23.358	<0.001*	0.642
Time	11	143	80.405	<0.001*	0.861
tDCS × emotion	2	52	0.732	0.574	0.053
tDCS × time	22	286	2.017	0.005*	0.134
Emotion × time	22	286	68.022	<0.001*	0.840
tDCS × emotion × time	44	572	1.520	0.019*	0.105
EXPERIMENT 2					
Standardized reaction times					
tDCS	2	40	2.964	0.063	0.129
Emotion	1	20	1.527	0.231	0.071
Time	4	80	18.713	<0.001*	0.483
tDCS × emotion	2	40	1.780	0.182	0.082
tDCS × time	8	160	1.444	0.182	0.067
Emotion × time	4	80	2.205	0.076	0.099
tDCS × emotion × time	8	160	1.159	0.327	0.055
Standardized correct answers					
tDCS	2	40	2.244	0.119	0.256
Emotion	1	20	1.884	0.185	0.086
Time	4	80	14.991	<0.001*	0.754
tDCS × emotion	2	40	0.542	0.586	0.053
tDCS × time	8	160	0.945	0.481	0.329
Emotion × time	4	80	2.237	0.072	0.287
tDCS × emotion × time	8	160	0.325	0.955	0.135

For the SES, ANOVAs were calculated for absolute and standardized values. For the emotional face identification task, ANOVAs were calculated for standardized reaction times and number of correct answers. The asterisks mark significant main effects and interactions. d.f., degrees of freedom; F, F-value; p, probability; η^2, effect size.

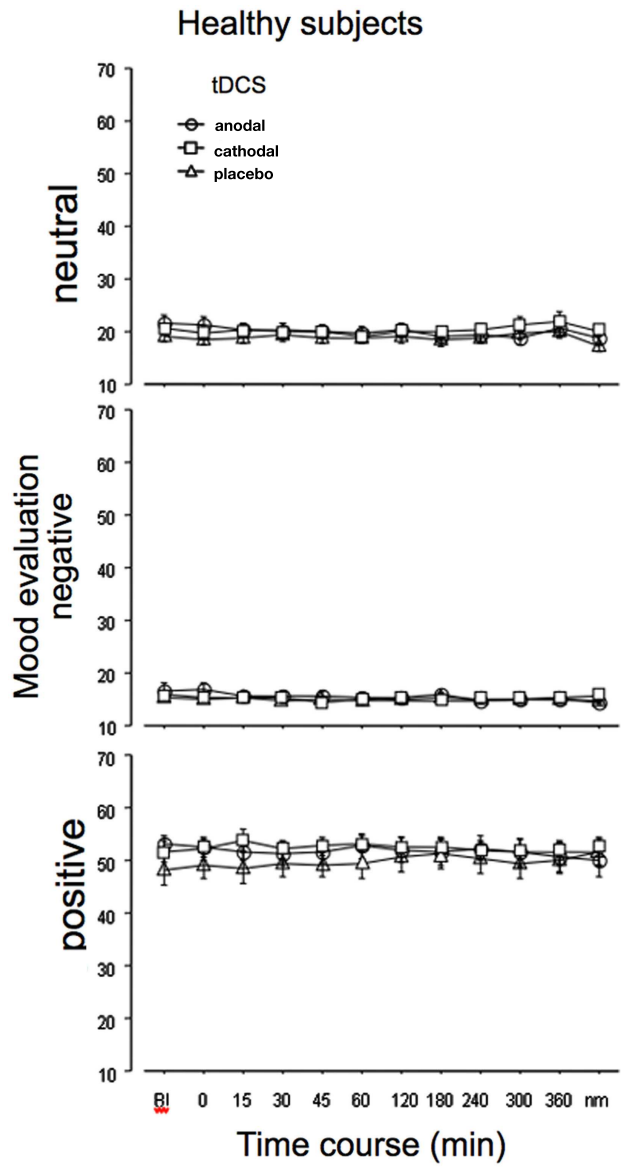

FIGURE 2 | Emotional state is not affected by tDCS in healthy subjects. Depicted are the absolute mean values before and up to the morning after anodal, cathodal, or sham tDCS over the left DLPFC for neutral (lethargic), negative, and positive emotional state, as measured by the adjective checklist SES. As can be seen from the results, the evaluation is quite stable in all stimulation conditions throughout the course of the experiment. The vertical bars indicate standard error of mean. nm, next morning.

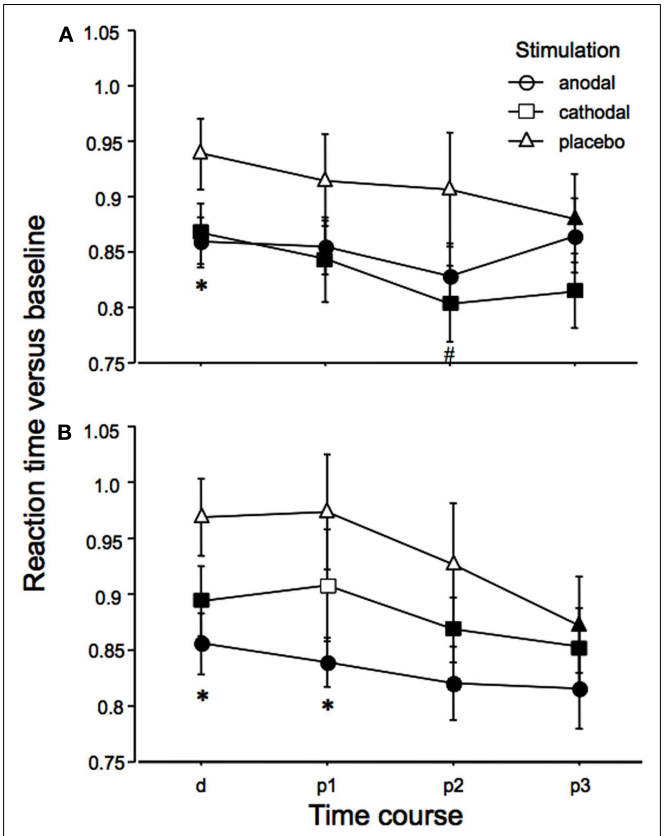

FIGURE 3 | Emotional face identification is modified by tDCS: reaction times. Baseline-standardized reaction times for the identification of the position of negative **(A)** or positive **(B)** emotional facial expressions shown on a computer screen are depicted during (d) and after (p1–3; p1 = immediately and 5 min after tDCS, p2 = 10 and 20 min after tDCS, p3 = 30 and 60 min after tDCS), anodal, cathodal, and placebo tDCS. Reaction times become faster during the course of the experiment, thus indicating learning of the task in all stimulation and emotional conditions. Under both real stimulation conditions and for both facial expressions, reaction time reductions become earlier significant than under placebo stimulation. Under anodal tDCS, positive emotional facial expressions are faster identified as compared to placebo stimulation during and after tDCS. For emotionally negative facial expressions, anodal tDCS improves perception only during tDCS as compared to placebo stimulation. A minor effect can be seen for cathodal tDCS, as compared to placebo stimulation (p2 only). Filled symbols indicate significant reaction time differences as compared to baseline values, asterisks significant differences between anodal tDCS and placebo tDCS, and hash symbols significant differences between cathodal and placebo tDCS for a given time point (paired, two-tailed t-tests, $p < 0.05$). Vertical bars indicate standard error of mean.

placebo stimulation. Anodal tDCS reduced reaction time significantly during tDCS relative to placebo stimulation for emotionally negative faces. For emotionally positive facial expressions, this effect emerged during tDCS, and remained significant for up to 10 min after tDCS. Reaction times under cathodal tDCS did differ significantly relative to placebo stimulation only for negative facial expressions during the second measures after tDCS.

Baseline performance was identical for all tDCS conditions in relation to one facial expression.

Correct answers

The ANOVA revealed a significant main effect of time (**Table 1**). As can be seen in **Figure 4**, this is caused by an increased number of correct answers relative to baseline in the later blocks of the task for all stimulation and facial expression conditions. For the placebo and anodal stimulation condition, but not for cathodal tDCS, this effect is significant during the whole time course of the experiment for the recognition of negative emotional facial expressions. For positive facial expressions, anodal tDCS caused a significant improvement as compared to baseline in the last two measures,

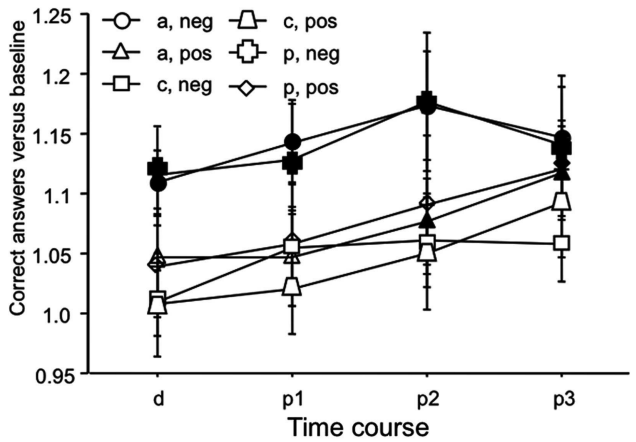

FIGURE 4 | Emotional face identification: number of correct trials. Baseline-standardized mean number of correct trials are depicted during, and after anodal, cathodal, and placebo tDCS (p1–3; p1 = immediately and 5 min after tDCS, p2 = 10 and 20 min after tDCS, p3 = 30 and 60 min after tDCS). The number of correct trials increases during the course of the experiment, thus indicating learning of the task in all stimulation and emotional conditions. This effect is significant for negative facial expressions under anodal and placebo tDCS conditions for the whole course of the experiment, but not for cathodal tDCS. For positive facial expressions, anodal tDCS caused a significant improvement as compared to baseline in the last two measures, and placebo tDCS in the last measure. Again under cathodal tDCS facial recognition did not improve significantly. Filled symbols indicate significant reaction time differences as compared to baseline values (paired, two-tailed *t*-tests, $p < 0.05$). Vertical bars indicate standard error of mean. a, anodal tDCS; c, cathodal tDCS; p, placebo tDCS; pos, positive emotional facial expression; neg, negative emotional facial expression.

and placebo tDCS in the last measure. Baseline values did not differ significantly between the respective stimulation conditions.

DISCUSSION

The results of this study suggest that tDCS of the prefrontal cortex has an impact on emotional state-related information processing in healthy subjects. tDCS of the left DLPFC improved emotional face recognition, most markedly for emotionally positive faces, and anodal tDCS. This effect, however, seems to be not accompanied by modifications of subjective emotional state, which was not affected by tDCS in Experiment 1. Therefore, the results are in favor for a dissociation of the impact of tDCS on self-referenced emotional state and state-related information processing in healthy subjects.

MISSING EFFECT OF PREFRONTAL tDCS ON EMOTIONAL STATE IN HEALTHY SUBJECTS

Anodal and cathodal tDCS of the left DLPFC, combined with antagonistic stimulation of the right supraorbital area, did not modulate emotional state, as rated by an adjective checklist. Positive, negative, and neutral ratings were identical in all conditions. Since negative and neutral – the latter representing lethargy – emotional state values were near the minimum throughout the experiment independent from stimulation condition, while positive mood was more in a medium range, one could suspect that social expectancy contributed to these results. However, the SES has been shown to be a reliable and valid instrument to measure emotional state in other studies (Scholz, 2001). This pattern of results is comparable to the effects of left DLPFC rTMS, and another tDCS study (Plazier et al., in press). It might be caused by a kind of ceiling effect preventing a further increase of positive emotional state and a floor effect for negative and lethargic emotional state in healthy subjects with normal activation of the DLPFC.

tDCS MODULATES EMOTION-RELATED INFORMATION PROCESSING

In general, the effects of tDCS on emotional face identification were relatively low, the results of the respective ANOVAs showed only a trendwise effect of tDCS. We nevertheless conducted exploratory *post hoc* tests to identify also slight tDCS-related alterations. These, however, should be confirmed in larger studies in future.

During the course of the experiment subjects were able to identify the position of the emotional non-neutral face faster, independent of stimulation condition, or mood quality, i.e., a learning process took place. This performance improvement tended to be larger for the real tDCS conditions. In principle this could be caused by an unspecific arousal effect of real tDCS as compared to placebo stimulation. However it was shown recently that placebo stimulation, as performed in our study, cannot be discerned from real stimulation by the subjects (Gandiga et al., 2006). Furthermore, former studies showed a highly stimulation polarity- and electrode position-dependent effect of tDCS. Moreover, tDCS did not induce arousal in our subjects, as shown by the results of the adjective checklist for the items representing lethargy. Thus unspecific arousal as the result of stimulation seems not a likely explanation. A tDCS-dependent alteration of attention can however not be excluded completely, since tDCS, although of other areas, has been shown to affect attentional processes (Bolognini et al., 2010).

The reaction time results, according to the results of the exploratory *post hoc* tests, moreover hint to a specific beneficial effect of anodal tDCS on recognition of positive and negative emotional facial expressions as compared to baseline values. This result, which is most probably due to improved information processing by excitability-enhancing anodal tDCS of the DLPFC, is in accordance with former studies. Here an involvement of the left DLPFC in the processing of affective material, especially emotionally valenced faces was described (Herrington et al., 2005; Sergerie et al., 2005; Grimm et al., 2006). For this, the impact of the DLPFC on the evaluation of accumulated information and response selection might be of importance (Badre and Wagner, 2004). Furthermore, as compared to placebo stimulation, the improvement of performance tended to be larger for the emotional positive facial expressions than for the negative ones. This result is in accordance with the fMRI study of Sergerie et al. (2005), where left DLPFC activation was enhanced by emotionally positive and negative faces, but to a larger degree by the positive faces. Thus the results of our study are compatible with the finding that the left DLPFC is involved in the processing of emotional valenced faces in general, but with an additional emphasis on positive emotions.

For reaction time, also under cathodal tDCS the results of the exploratory *post hoc* tests show a – somewhat weaker – effect for improved performance relative to placebo stimulation. This might be caused by a slight improvement of information processing induced by general network excitability reduction, which has a focusing effect on perception, as demonstrated in former studies (Antal et al., 2004). Alternatively, since due to the electrode arrangement left DLPFC stimulation was inevitably associated with right prefrontal tDCS, and the right prefrontal cortex is also involved in affective information processing (Herrington et al., 2005; Kensinger and Schacter, 2006), the accompanying anodal right prefrontal tDCS might have contributed.

With regard to the number of correct identifications of the emotional facial expression, an increase takes place throughout the course of the experiment, which is significant relative to baseline for the latest measures under anodal and placebo tDCS for positive and negative emotional expressions, as shown by the exploratory *post hoc* tests. Negative facial expressions were significantly better recognized, as compared to baseline, also in earlier blocks for anodal and placebo stimulation. However, under cathodal tDCS the amount of correctly identified faces did not significantly improve for both emotional qualities relative to baseline. This pattern of results is in favor for a relative decrease of the ability of the subjects to identify emotional facial expressions under a cortical excitability diminution, as delivered by cathodal tDCS. While at first sight this result seems to contradict the reaction time results under cathodal tDCS, it might be explained as follows: the overall excitability reduction will impair the ability to correctly identify a facial expression, but, once identified, enhance reaction time via focusing cortical activity.

GENERAL REMARKS

Taken together, the results of the experiments are compatible with a dissociation of the effects of left DLPFC stimulation on self-referenced emotional state and emotion-related information processing. Whereas in the healthy subjects emotional state was not modulated, the identification of facial expression of emotions was improved by tDCS. This assumed dissociation is in line with the current state of research, since it has been shown that for the prefrontal cortex, the medial inferior prefrontal cortex is mainly involved in self-referenced emotion, while cognitive functions are localized predominantly in the DLPFC (Steele and Lawrie, 2004). However, since it has also been shown that both areas are functionally overlapping, it makes sense that the DLPFC might be involved in cognitive processing of emotional material. A limitation of Experiment 2 is that emotional state has not been tested in this experiment. Thus it cannot be ruled out completely that the emotional state of the subjects differed systematically between the respective experimental sessions, and that such differences have affected the results of this experiment.

With regard to the facial recognition task, the results of our study are furthermore in favor for a larger involvement of the left DLPFC in the identification of affective positive than of affective negative faces. This is in line with the notion that the left hemisphere is more involved in positive than in negative emotions. It is proposed that left hemispheric brain tumors and epilepsies are associated with depression, while tumors of the right hemisphere cause euphoric mood (Perini, 1986; Belyi, 1987). Moreover, happy mood and presentation of emotionally positive stimuli produce stronger activation of the left prefrontal cortex in healthy subjects (Habel et al., 2005; Herrington et al., 2005; Sergerie et al., 2005). Facial recognition, however, was also improved – but to a smaller degree – for emotionally negative faces by tDCS. This effect might be caused by an additional involvement of the DLPFC in facial recognition, which is independent from a specific emotional quality (Kilts et al., 2003; Sergerie et al., 2005; Pavuluri et al., 2006; Schutter and van Honk, 2006).

The failure of excitability-enhancing tDCS of the left DLPFC to induce positive mood in healthy subjects is surprising at first sight, because this stimulation protocol improved mood in a group of depressed subjects relevantly in a former study (Fregni et al., 2006). It is however in accordance with the results of a recently published study of another group (Plazier et al., in press). Moreover, also rTMS protocols that were effective to improve mood in depression failed to have the same effect in healthy subjects (Mosimann et al., 2000; Baeken et al., 2006).

The present study delivers indirect hints for a dissociation of emotion-related information processing and self-referenced emotional state. The results are in favor for the hypothesis that the DLPFC might be more involved in the cognitive aspects of emotional processing. To influence emotional state more directly by external stimulation techniques, it might be promising to study other prefrontal areas, such as the inferior-medial prefrontal cortex, which seem to be critically involved in the production of emotions (Steele and Lawrie, 2004) in future studies.

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APPENDIX

Table A1 | Here the results of the *post hoc* Student's *t*-tests conducted on standardized reaction times and error rate of Experiment 2 are shown.

	Mean value	Confidence intervals – lower bound	Confidence intervals – upper bound	*t*-Value	*P*
STANDARDIZED REACTION TIMES					
vs BL					
d a pos	0.14	0.09	0.2	5.25	<0.001
p1 a pos	0.16	0.11	0.2	7.21	<0.001
p2 a pos	0.18	0.11	0.25	5.42	<0.001
p3 a pos	0.19	0.11	0.26	5.34	<0.001
da neg	0.14	0.10	0.19	6.25	<0.001
p1 a neg	0.15	0.10	0.20	6.02	<0.001
p2 a neg	0.17	0.11	0.23	5.91	<0.001
p3 a neg	0.14	0.07	0.21	4.03	0.001
d c pos	0.11	0.04	0.17	3.39	0.03
p1 c pos	0.09	0.01	0.19	1.84	0.081
p2 c pos	0.13	0.07	0.20	4.50	<0.001
p3 c pos	0.15	0.07	0.22	4.24	<0.001
dc neg	0.13	0.08	0.19	4.87	<0.001
p1 c neg	0.16	0.08	0.24	4.05	<0.001
p2 c neg	0.20	0.12	0.27	5.64	0.001
p3 c neg	0.19	0.11	0.26	5.48	<0.001
ds pos	0.03	0.04	0.10	0.91	0.37
p1 s pos	0.03	0.08	0.13	0.52	0.61
p2 s pos	0.07	0.04	0.19	1.35	0.19
p3 s pos	0.13	0.04	0.22	2.95	0.008
d s neg	0.06	0.01	0.13	1.91	0.071
p1 s neg	0.09	0.01	0.17	2.07	0.051
p2 s neg	0.09	0.01	0.20	1.81	0.085
p3 s neg	0.12	0.04	0.20	3.04	0.007
vs sham					
d a pos	0.11	0.21	0.02	2.51	0.021
p1 a pos	0.11	0.25	0.02	1.86	0.077
p2 a pos	0.11	0.22	0.01	2.01	0.059
p3 a pos	0.06	0.16	0.04	1.18	0.251
d a neg	0.08	0.15	0.01	2.39	0.027
p1 a neg	0.06	0.15	0.03	1.36	0.189
p2 a neg	0.08	0.17	0.02	1.68	0.109
p3 a neg	0.02	0.10	0.07	0.38	0.708
d c pos	0.08	0.18	0.03	1.50	0.150
p1 c pos	0.06	0.20	0.07	1.00	0.329
p2 c pos	0.06	0.17	0.06	1.07	0.299
p3 c pos	0.01	0.10	0.06	0.49	0.628
d c neg	0.07	0.17	0.02	1.57	0.132
p1 c neg	0.07	0.17	0.03	1.47	0.157
p2 c neg	0.1	0.20	0.01	2.14	0.045
p3 c neg	0.07	0.14	0.01	1.71	0.104
STANDARDIZED ERRORS					
vs BL					
d a pos	0.05	0.13	0.04	1.18	0.253
p1 a pos	0.05	0.13	0.04	1.16	0.260
p2 a pos	0.08	0.15	0.01	2.13	0.045
p3 a pos	0.12	0.20	0.03	3.00	0.008

(Continued)

Table A1 | Continued

	Mean value	Confidence intervals – lower bound	Confidence intervals – upper bound	*t*-Value	*P*
d a neg	0.11	0.17	0.05	4.13	0.001
p1 a neg	0.14	0.22	0.07	4.11	0.001
p2 a neg	0.17	0.27	0.08	3.82	0.001
p3 a neg	0.14	0.26	0.04	2.80	0.011
d c pos	0.01	0.10	0.08	0.17	0.867
p1 c pos	0.02	0.10	0.06	0.54	0.595
p2 c pos	0.05	0.15	0.05	1.07	0.297
p3 c pos	0.09	0.19	0.01	2.04	0.054
d c neg	0.01	0.06	0.05	0.33	0.747
p1 c neg	0.06	0.13	0.02	1.63	0.119
p2 c neg	0.06	0.14	0.02	1.56	0.135
p3 c neg	0.06	0.12	0.01	1.89	0.006
d s pos	0.04	0.13	0.05	0.93	0.362
p1 s pos	0.06	0.17	0.05	1.12	0.276
p2 s pos	0.09	0.21	0.03	1.56	0.135
p3 s pos	0.12	0.20	0.04	3.07	0.006
d s neg	0.12	0.20	0.03	2.79	0.011
p1 s neg	0.13	0.22	0.03	2.80	0.011
p2 s neg	0.18	0.30	0.06	3.05	0.006
p3 s neg	0.14	0.24	0.04	3.00	0.008
vs sham					
d a pos	0.01	0.14	0.15	0.11	0.910
p1 a pos	0.01	0.12	0.10	0.22	0.830
p2 a pos	0.01	0.13	0.11	0.23	0.823
p3 a pos	0.01	0.09	0.08	0.09	0.926
d a neg	0.01	0.11	0.10	0.09	0.926
p1 a neg	0.01	0.11	0.14	0.23	0.823
p2 a neg	0.01	0.14	0.14	0.05	0.964
p3 a neg	0.01	0.14	0.15	0.08	0.936
d c pos	0.03	0.14	0.08	0.59	0.559
p1 c pos	0.04	0.15	0.08	0.69	0.498
p2 c pos	0.04	0.18	0.10	0.51	0.617
p3 c pos	0.03	0.15	0.09	0.52	0.607
d c neg	0.11	0.21	0.01	2.072	0.051
p1 c neg	0.07	0.19	0.08	1.28	0.215
p2 c neg	0.12	0.26	0.03	1.66	0.112
p3 c neg	0.08	0.19	0.03	1.54	0.140

d, During tDCS; p1, first measure post-tDCS; p2, second measure post-tDCS; p3, third measure post-tDCS; a, anodal tDCS; c, cathodal tDCS; s, sham tDCS.

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Transcranial direct current stimulation of the frontal eye fields during pro- and antisaccade tasks

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Transcranial direct current stimulation (tDCS) has been successfully applied to cortical areas such as the motor cortex and visual cortex. In the present study, we examined whether tDCS can reach and selectively modulate the excitability of the frontal eye field (FEF). In order to assess potential effects of tDCS, we measured saccade latency, landing point, and its variability in a simple prosaccade task and in an antisaccade task. In the prosaccade task, we found that anodal tDCS shortened the latency of saccades to a contralateral visual cue. However, cathodal tDCS did not show a significant modulation of saccade latency. In the antisaccade task, on the other hand, we found that the latency for ipsilateral antisaccades was prolonged during the stimulation, whereas anodal stimulation did not modulate the latency of antisaccades. In addition, anodal tDCS reduced the erroneous saccades toward the contralateral visual cue. These results in the antisaccade task suggest that tDCS modulates the function of FEF to suppress reflexive saccades to the contralateral visual cue. Both in the prosaccade and antisaccade tasks, we did not find any effect of tDCS on saccade landing point or its variability. Our present study is the first to show effects of tDCS over FEF and opens the possibility of applying tDCS for studying the functions of FEF in oculomotor and attentional performance.

Keywords: saccade, antisaccade, frontal eyefield, transcranial direct current stimulation

INTRODUCTION

Delivering direct current from scalp to cortex over several minutes has been shown to induce a long-lasting change in cortical excitability. This stimulation technique called transcranial direct current stimulation (tDCS) has been applied to many cortical areas, most notably the motor cortex (Priori et al., 1998; Nitsche and Paulus, 2000, 2001; Baudewig et al., 2001) and visual cortical areas (Antal et al., 2003, 2004, 2006). In tDCS, anodal stimulation generally enhances cortical excitability and cathodal stimulation suppresses it. TDCS is believed to interfere with brain functions by modulating the spontaneous firing rate of the cortex under the stimulating electrode by depolarizing the membrane potential with anodal stimulation or by hyperpolarizing it with cathodal stimulation (Bindman et al., 1962; Creutzfeldt et al., 1962; Fregni and Pascual-Leone, 2007). For example, motor-evoked potentials (MEP) in response to transcranial magnetic stimulation (TMS) over the motor cortex become larger after anodal stimulation, while they are reduced following cathodal stimulation (Nitsche and Paulus, 2000, 2001). An analogous study on the visual cortex showed a similar pattern of results: Antal et al. (2003) measured excitability of the visual cortex by measuring the TMS-induced phosphene threshold over the occipital cortex following anodal or cathodal stimulation. Consistent with the results for the motor cortex, the phosphene threshold decreased after anodal stimulation and increased after cathodal stimulation.

The goal of the present study was to examine whether tDCS can reach and modulate the excitability of the frontal eye fields (FEF), which is one of the key areas involved in controlling eye movements and selective attention (Robinson and Fuchs, 1969; Mohler et al., 1973; Wurtz and Mohler, 1976; Schall and Thompson, 1999; Serences and Yantis, 2007). Since no study has targeted FEF with tDCS to date, our primary goal was to observe possible effects of tDCS over FEF. Toward this goal, our first set of experiments examined how tDCS over the FEF modulates saccade properties in a simple prosaccade task in which subjects are required to make an eye movement toward a peripheral stimulus. The FEF in each hemisphere is known to be involved in the control of saccades in the contralateral direction. Since saccade latency is known to be dependent on the time when the firing rate of FEF reaches a threshold for saccade execution (Hanes and Schall, 1996), it was expected that the firing rate in FEF would reach the threshold for saccade execution more quickly if the baseline firing rate was increased by anodal tDCS. Conversely, suppression of the firing rate in FEF was expected to prolong the saccade latency. Alternatively, saccade latency can be modulated by changes in the threshold for saccade generation (Reddi et al., 2003). Thus, it is also conceivable that tDCS modulates saccade latency by changing the threshold rather than changing the baseline activity level.

There are several lines of evidence that impairment or inactivation of the FEF prolongs saccade latency in the prosaccade task. Patients with lesions in the FEF show a prolonged latency for prosaccades toward the direction contralateral to the lesion in an overlap condition in which the initial fixation point remained displayed even after the saccade target appeared (Gaymard et al.,

Abbreviations: BOLD, blood-oxygen-level dependent; FEF, frontal eye field; MEP, motor-evoked potential; rTMS, repetitive TMS; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

1999). In monkeys, acute inactivation of the FEF leads to a prolongation of saccade latency in the direction contralateral to the inactivated FEF (Sommer and Tehovnik, 1997; Dias and Segraves, 1999). Small prolongation of ipsilateral saccades was also reported, but this effect was much smaller than the effects on contralateral saccades. Previous TMS studies show that the saccade latency in the prosaccade task is increased following 10 min of offline 1 Hz repetitive TMS (rTMS) or theta burst stimulation over FEF (Nyffeler et al., 2006a,b). These studies together suggest that activity in FEF influences the latency of prosaccades.

In the second part of our study, we examined possible effects of tDCS over FEF in the antisaccade task (Hallet, 1978) in which subjects are required to suppress reflexive eye movement to a visual cue and generate a volitional saccade to the location opposite to the cue (for reviews, see Everling and Fischer, 1998; Munoz and Everling, 2004). FEF has been thought to play an important role in producing successful antisaccades. Earlier neuroimaging studies show that the activation of FEF is greater during blocks of antisaccade trials as compared to blocks of prosaccade trials or fixation (O'Driscoll et al., 1995; Müri et al., 1998; McDowell et al., 2002; Matsuda et al., 2004).

One important role of FEF in the antisaccade task is the generation of volitional saccades. Patients with a localized lesion in FEF show a normal percentage of errors in suppressing reflexive saccades, whereas the latency of correct antisaccades was increased bilaterally (Pierrot-Deseilligny et al., 1991; Rivaud et al., 1994; Gaymard et al., 1999). Neuroimaging studies using an event-related design showed that the activity of FEF is strongly associated with the generation of a volitional saccade (Ettinger et al., 2008). On the other hand, FEF is also implicated in the suppression of reflexive saccades (Hunt et al., 2004). Patients with lesions to FEF and possibly other frontal areas, including the dorsolateral prefrontal cortex, have difficulty in suppressing reflexive saccades in the antisaccade task (Guitton et al., 1985). Neuroimaging studies in which the prosaccade and antisaccade trials were randomly assigned by a visual cue showed differential BOLD activity in FEF even before the appearance of the saccade target. Therefore, the enhanced activity in the FEF after the instruction for an antisaccade was interpreted as reflecting the preparatory set for suppressing a response to the upcoming saccade target (Connolly et al., 2002; Cornelissen et al., 2002). We discuss our results of tDCS over FEF in the antisaccade task in the context of these two FEF functions, namely, generation of volitional saccades and suppression of reflexive saccades.

MATERIALS AND METHODS

PROSACCADE TASK WITH BILATERAL tDCS

Subjects

Sixteen subjects (6 males and 10 females) were recruited from the community of University College London. They were all right-handed and had normal or corrected-to-normal visual acuity. Informed written consent was obtained from each participant. During the experiment, they sat 57 cm away from a 17″ CRT monitor running with a 100-Hz refresh rate. Their head was immobilized by a chin- and headrest on which an eyetracker (Eyelink, SMI, Berlin/Germany) was mounted. The experiment conformed to the Declaration of Helsinki and was approved by a local (University College London) ethical committee. Informed consent was obtained from all subjects.

Transcranial direct current stimulation

Direct current was delivered by a constant current stimulator (Schneider Electronics, Gleichen, Germany) via a pair of anodal and cathodal electrodes placed over left and right FEF. The electrodes were covered with flat synthetic sponges soaked in 0.9% NaCl solution. The contact surface of the sponges was 3 cm × 3 cm for both electrodes. The maximum current density under the electrode was 0.11 mA/cm^2. This is slightly higher than typical current density ranging 0.029 and 0.08 mA/cm^2 (Nitsche et al., 2008) and was chosen in order to increase the focality and effectiveness of the stimulation (i.e., the area of the electrode was lower than that typically used). The electrodes were fixed to the target positions (see below) with rubber bands. The intensity of tDCS was slowly ramped up to 500 μA over the initial 10 s of stimulation. If participants felt comfortable with the stimulation, we further increased the intensity up to 1000 μA and continued the stimulation for 10 min. Typically the voltage required to achieve 1000 μA stimulation without unpleasant sensations was below 20 V. If participants reported any unpleasant sensation at the scalp under the electrodes (usually the anodal electrode), we added saline to the sponge and waited until the impedance between the electrodes decreased.

Localization of FEF

Structural MRI images of all participants were obtained prior to the experiment. The positions of left FEF and right FEF were determined for individual participants using FSL (FMRIB Software Library, Oxford, UK) in the following transformation steps; first we converted individual structural images to the standard MNI coordinates, and then the coordinates for left FEF and right FEF in MNI coordinates were transformed back to the real image space. The MNI coordinates for L-FEF and R-FEF were (−32.3, −4.4, 49.8) and (31.3, −4.5, 50.9). Those values are calculated from the Talairach coordinate given in Paus (1996) by converting the coordinates from Talairach space to MNI space. The individual specific target sites were used to guide frameless stereotaxy using the Brainsight system (Rogue Research, Montreal, Canada).

While it is known that the exact location of FEF can be variable between individuals, our approach of targeting FEF using the standard coordinate has proved to be sufficiently effective for interfering with functions of FEF (e.g., Muggleton et al., 2003; Juan et al., 2008; Nuding et al., 2009; Bardi et al., 2012). A recent study compared three different types of neuronavigation methods by comparing effects of TMS over the parietal cortex using individual fMRI results, the standard coordinate and the P4 of the international 10–20 system (Sack et al., 2009). The study showed that the fMRI-based neuronavigation is more effective, but the standard coordinate was also effective if about twice as many subjects were tested. On the other hand, neuronavigation based on the 10–20 system required many more subjects (about 10 fold more) to reach comparable statistical power. Thus, given the number of subjects in each of our experiment ($n = 16$ for each experiment), we expected that a coordinate based approach without fMRI validation would be sufficient for our purpose. Moreover, the electric current delivered through the scalp spreads very rapidly and the

electrode sponges cover a large area (3 cm × 3 m) relative to TMS. We chose the coordinate based approach to target FEF, because we did not expect precise localization of FEF for individual subjects separately would improve the effectiveness of tDCS due to the relatively large electrodes and volume conduction of the current used in this technique.

Design of the experiment

The task for the participants was to make an eye movement to a target (black square) in response to the onset of the target presented in one of two designated positions (8.1° away from the fixation horizontally), which were indicated by hollow square frames (**Figure 1A**). The target position (left or right) was randomized across trials, and the participants completed 40 trials in one block. Each block was completed within 5 min including calibration of the eye tracker at the beginning of each block.

The central fixation point remained on the screen even after the saccade target appeared. In a study of FEF patients, no impairment was found in a gap condition in which the initial fixation point was removed 200 ms before the onset of the saccade target (Pierrot-Deseilligny et al., 1991; Rivaud et al., 1994). In order to observe possible effects of tDCS over the FEF, we therefore used the overlap paradigm for the prosaccade experiment as described above.

First, each participant completed one practice block of 40 trials before starting the actual experimental session. After the practice, participants completed a session consisting of five pairs of blocks (10 blocks in total; see **Figure 1B**). The first pair of blocks (Blocks 1 and 2) were the baseline condition to which subsequent performance was compared. TDCS was delivered during the second pair of blocks (Blocks 3 and 4) for 10 min. The third, fourth, and fifth pairs were used to estimate long-lasting effects of tDCS on saccade properties during 0–10, 10–20, and 20–30 min following the termination of tDCS, respectively. At the beginning of each block, the eye tracker was calibrated and drift correction was performed at the beginning of each trial.

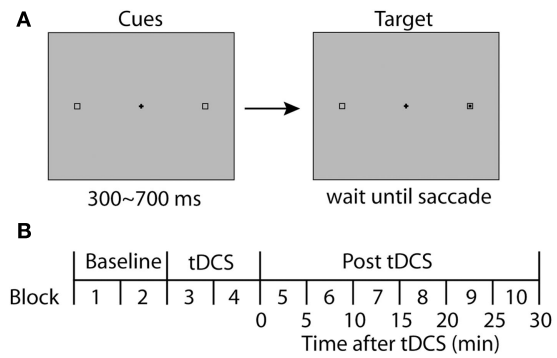

FIGURE 1 | Experimental design. (A) Stimulus display for a single trial is illustrated. Two boxes were displayed continuously throughout a trial. A black square appeared within one of the boxes after a variable delay (300–700 ms). In the prosaccade experiments, subjects were asked to make direct their gaze to the visual target as quickly and accurately as possible. In the antisaccade task, they were asked to make an eye movement away from the visual cue, directing to the square on the opposite side. **(B)** The time course of an experimental session. A session started with two blocks of baseline conditions before tDCS, followed by another two blocks with tDCS. After the tDCS blocks, six more blocks were completed to observe the time course of possible effects of tDCS. Each block duration was adjusted to be 5 min including the calibration of the eye tracker and a brief rest between blocks.

For half of the participants, the anodal electrode was placed over left FEF and cathodal over right FEF, and the polarity of the electrodes was reversed for the other half of the participants. Saccade data were analyzed according to whether saccade direction was contralateral to the anode or the cathode.

Eye movement recording and analysis

The gaze direction of the right eye was sampled at 250Hz using EyeLink system (SR Research Ltd, Ontario, Canada). We calculated saccade latency, landing position with respect to the target and variability of saccade amplitudes. To determine the onset and offset of a saccade, we used a velocity criterion. When eye velocity exceeded 26.8°/s, that time point was regarded as the onset of a saccade and when eye velocity went down again below 26.8 deg/s, the time point immediately after this sample was regarded as the termination of the saccade. Data points for saccade latencies, amplitudes, and landing positions were collapsed across two consecutive 5 min sessions (40 trials ×2) in order to increase the robustness of estimating these parameters.

Median rather than mean was used for saccade latency because the distribution of saccade latencies is typically skewed (e.g., Carpenter and Williams, 1995). However, the results of statistical analysis showed qualitatively identical patterns when the mean saccade latency was used. In the present paper, we report only the results of median based latency estimates.

Trials were rejected from the analyses if eye position at the time of target onset deviated from the fixation more than 1.8°, if the first saccade after target onset was directed to the opposite side from the target, or if saccade latency was longer than 400 ms or shorter than 50 ms. Trials were sorted according to whether saccade direction was contralateral to anode position or cathode position.

PROSACCADE TASK WITH UNILATERAL tDCS

Subjects

Sixteen new subjects participated in the cathode only condition (5 males and 11 females), and yet another 16 subjects (8 males and 8 females) participated in the anode only condition. None of them had participated in the bilateral tDCS experiment. The experiment conformed to the Declaration of Helsinki and was approved by a local (University College London) ethical committee. Informed consent was obtained from all subjects.

Design of the experiments

The experiments were conducted in the same manner as the first experiment. Both for the anodal experiment and cathodal experiment, half of subjects in each experiment had tDCS on the right side and the other half on the left. Data were sorted according to whether saccade target appeared contralateral to the tDCS site.

Transcranial direct current stimulation

The duration and intensity parameters were identical to the bilateral experiment. When stimulating the motor cortex with tDCS,

reference electrodes are often placed on the contralateral forehead because other electrode montages were found to be ineffective (Nitsche and Paulus, 2000). However, we avoided using the forehead position for the reference electrode in order to avoid unexpected effects of stimulating the cortical structures under the reference electrode, as comparisons would be made between contralateral and ipisilateral saccades in our experiment. Therefore, the reference was fixed on the shoulder ipsilateral to the stimulation electrode, a montage known to be effective for stimulating the motor cortex (Priori et al., 1998). For the reference electrode, we used a larger electrode (5 cm × 7 cm) to minimize the current density and thereby sensation on the skin. No sham condition was included in this study.

ANTISACCADE TASK WITH UNILATERAL tDCS

Subjects

As in the prosaccade experiment with unilateral tDCS, 16 subjects participated in the cathode only condition, and another 16 subjects participated in the anode only condition. Three of participants who took part in the cathode condition took part also in the prosaccade experiment (two of them were in the anode condition and one of them was in the cathode condition). Three participants in the anode condition took part also in the prosaccade experiment (two of them were in the anode condition and one of them was in the cathode condition). However, these two experiments involved different tasks and were conducted at least 6 months apart and therefore carry-over and practice effects are expected to be negligible. The experiment conformed to the Declaration of Helsinki and was approved by a local (University College London) ethical committee. Informed consent was obtained from all subjects.

Design of the experiments

The stimuli were identical to the prosaccade experiments described above. The only difference was that the subjects were instructed to make a saccade to the box opposite to the black cue. Both for the anodal experiment and cathodal experiment, half of subjects in each experiment had tDCS on the right side and the other half on the left. Data were sorted according to whether the correct saccade direction was contralateral or ipsilateral to the tDCS site. The stimulation methods for tDCS were identical to the prosaccade experiment with unilateral tDCS described above. No sham condition was included in this study.

RESULTS

BILATERAL tDCS OVER FEF IN THE PROSACCADE TASK

In the first experiment, we applied tDCS bilaterally with anode over one FEF and cathode over the other. Since anode and cathode often produce opposite effects, we expected this bilateral tDCS configuration would yield a large difference between leftward and rightward saccade properties if any effect was to be observed.

The time course of saccade latency is shown in **Figure 2A**. In order to estimate effects of tDCS and the time course of any effects, we subtracted the baseline saccade latency obtained before tDCS from the data obtained in the subsequent tDCS session and post-tDCS sessions (**Figure 2D**). The shifts of saccade latency from the baseline were analyzed using ANOVA with the polarity of tDCS and time course as factors. We found a main effect of tDCS ($F(1,45) = 9.62$, $p < 0.01$). Time course was not significant ($F(3,45) < 1$) and there was no interaction between the two factors F(3,45) < 1). These results indicate that the latency of saccades in the direction contralateral to anodal tDCS became shorter than that of saccades contralateral to cathodal tDCS. These results suggest that anodal tDCS facilitated contralateral saccade generation and/or cathodal tDCS suppressed contralateral saccade generation.

In order to examine whether other metrics of saccades were altered by tDCS, we used two measures to estimate accuracy of saccades. One was the variability of the saccade landing point, which we calculated as the standard deviation of the horizontal position of the saccade landing point. The other measure was the mean landing position with respect to the target position. These two measures, variability and landing position, are indicative of the level of noise and systematic bias in saccade execution, respectively (e.g., White et al., 1994).

There were no statistically significant effects of anodal or cathodal stimulation on accuracy or variability. For the landing point of saccades, a repeated measures ANOVA with tDCS and time course as factors did not show any significant effect on the landing point (tDCS, $F(1,45) < 1$; time course, $F(3,45) = 1.19$, $p = 0.326$; interaction, $F(3,45) = 1.71$, $p = 0.178$). For the variability of saccade amplitude, a repeated measures ANOVA with tDCS and time course as factors did not show any significant effect on the variability (tDCS, $F(1,45) = 2.997$, $p = 0.104$; time course $F(3,45) < 1$; interaction, $F(3,45) < 1$).

These results together show that tDCS primarily influences saccade latency but has no effect on saccade amplitude or its variability. The effect on latency was specific to saccades contralateral to the FEF stimulated by the anode, suggesting that anodal stimulation shortened saccade latency. The latency difference produced by tDCS was 7.8 ms on average across the entire time course of the experiment. However, it is unclear whether the change in saccade latency was due to the anodal stimulation only, or alternatively was caused by a combination of anodal and cathodal effects, which shifted the balance between the left and right FEF.

UNILATERAL tDCS OVER FEF IN THE PROSACCADE TASK

In order to isolate effects of anodal and cathodal tDCS, we applied either anodal or cathodal tDCS over one FEF with the reference electrode over the ipisilateral shoulder (deltoid muscle).

The results of anodal tDCS are shown in **Figure 2B**. As in the bilateral experiment, we assessed the effects of tDCS by subtracting the baseline obtained before the tDCS delivery (**Figure 2E**). Consistent with the bilateral tDCS experiment, anodal stimulation shortened the latency of saccade contralateral to the stimulation site ($F(1,45) = 4.70$, $p < 0.05$). As in the bilateral experiment, we did not find a significant main effect of the time course ($F(3,45) = 1.25$, $p = 0.304$) nor an interaction between time course and saccade direction with respect to the stimulation site ($F(3,45) < 1$). The difference in saccade latency between tDCS and unstimulated sites was 6.4 ms. Neither the landing position nor its variability were affected by tDCS (all F-values <1 except the effect of tDCS on saccade variability, $F(1,45) = 2.07$, $p = 0.170$).

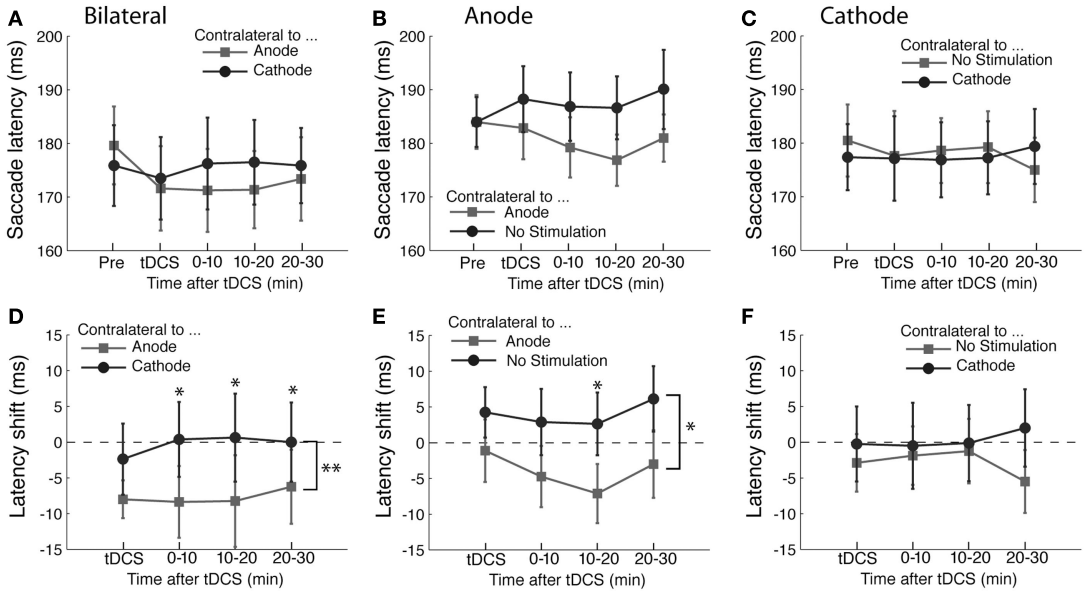

FIGURE 2 | Effects of tDCS in the prosaccade task. (A–C) The mean saccade latency is plotted as a function of the time course for the **(A)** bilateral, **(B)** anodal only, and **(C)** cathodal only conditions. **(D–F)** Shifts in saccade latency from the baseline condition before tDCS are plotted as a function of time from the beginning of tDCS blocks for saccades. In **(A)** and **(D)**, the light gray squares represent the latency of saccade contralateral to the anode and the dark gray circles the latency contralateral to the cathode. In **(B)** and **(E)**, the light gray squares represent the latency of saccade contralateral to the anode and the dark gray circles the latency contralateral to the unstimulated side. In **(C)** and **(F)**, the light gray squares represent the latency of saccade contralateral to the unstimulated side and the dark gray circles the latency contralateral to the cathode. The error bars correspond to one standard error of the mean (SEM). Asterisks ($*p < 0.05$ and $**p < 0.01$) indicate main effects of saccade direction with respect to stimulation site **(D,E)** and the significantly different pairs revealed by a *post hoc* two-tailed *t*-test test with Bonferroni correction.

The time course of saccade latency in the experiment with cathodal tDCS is shown in **Figure 2C**. As in the bilateral experiment, we analyzed the change in saccade latency with respect to the baseline obtained before the tDCS delivery (**Figure 2F**). There was no significant difference in saccade latency between the direction contralateral to tDCS side and the direction contralateral to the unstimulated side ($F(1,45) = 1.09$, $p = 0.313$). Neither was there an effect of time course ($F(3,45) < 1$) nor an interaction between time course and saccade direction with respect to stimulation site ($F(3,45) < 1$). Accuracy measures (i.e., variability and landing point) did not show a significant shift after cathodal tDCS either. The results of ANOVA on variability were non-significant for the effect of saccade direction with respect to the stimulation site ($F(1,45) = 2.68$, $p = 0.12$), time course ($F(3,45) < 1$) and interaction ($F(3,45) = 1.24$, $p = 0.31$). As for the landing point, there were no statistically significant effects of saccade direction ($F(1,45) = 1.1$, $p = 0.31$), time course ($F(3,45) < 1$) or their interaction ($F(3,45) = 1.68$, $p = 0.19$). Therefore, unilateral cathodal stimulation over FEF did not have any effect on saccade properties analyzed in the present study. This suggests that the effect of bilateral tDCS we found in the prosaccade experiment 1 was likely due to the anodal stimulation rather than cathodal stimulation. Thus, a lack of tDCS effects in unilateral conditions (e.g., cathodal tDCS in the prosaccade experiment) could be attributed to attenuation of tDCS effects rather than genuine absence of effects.

UNILATERAL tDCS OVER FEF IN THE ANTISACCADE TASK

The results of the antisaccade experiment are shown in **Figure 3**. The results of anodal tDCS are summarized in **Figures 3A,C**. Unlike the prosaccade experiments, we did not find any statistically significant effects of anodal tDCS in the antisaccade task. ANOVA on saccade latency showed a main effect of time course ($F(3,45) = 3.11$, $p < 0.05$), but there was no effect of tDCS ($F(1,45) < 1$) or interaction between time and tDCS condition ($F(3,45) < 1$). We did not find systematic effects of anodal tDCS on the variability of saccade amplitudes (Time, $F(3,45) < 1$; tDCS, $F(1,45) = 1.78$, $p = 0.20$; interaction, $F(3,45) < 1$) nor saccade landing points (Time, $F(3,45) = 2.26$, $p = 0.09$; tDCS, $F(1,45) < 1$; interaction, $F(3,45) = 1.53$, $p = 0.21$).

On the other hand, cathodal tDCS had an effect in the antisaccade task (**Figures 3B,D**). ANOVA on saccade latency revealed a significant interaction between time and tDCS condition ($F(3,45) = 3.45$, $p < 0.05$). This interaction was a result of the difference in latency during tDCS ($T(15) = -4.13$, $p < 0.01$). This indicates that ipsilateral antisaccades were delayed by cathodal tDCS compared with contralateral antisaccades (**Figure 3B**). The difference was not significant at any other time points (all T-values < 1). Both the factors of time course ($F(3,45) < 1$) and saccade direction with respect to stimulation site ($F(1,45) = 1.53$, $p = 0.24$) were statistically significant. We did not find any systematic effects of cathodal tDCS on other saccade metrics as the variability of saccade amplitudes (time course, $F(3,45) < 1$;

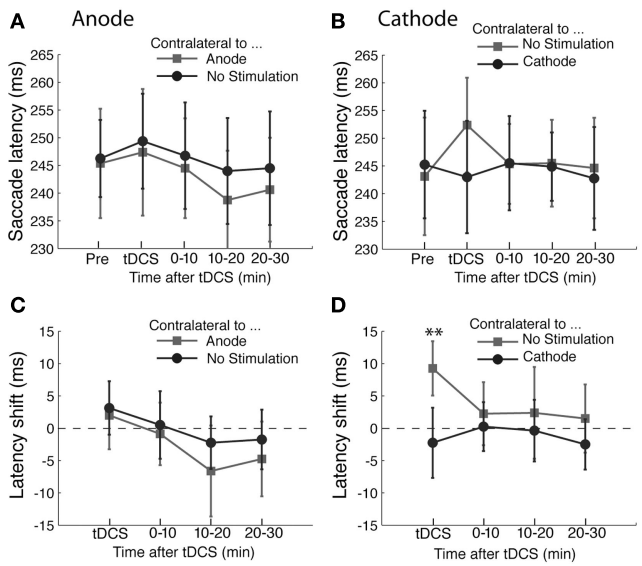

FIGURE 3 | Effects of tDCS in the antisaccade task. (A,B) The mean saccade latency is plotted as a function of the time course for the **(A)** anodal only and **(B)** cathodal only conditions. **(C,D)** Shifts in saccade latency from the baseline condition before tDCS are plotted as a function of time from the beginning of tDCS blocks for saccades. In **(A)** and **(C)**, the light gray squares represent the latency of saccade contralateral to the anode and the dark gray circles the latency contralateral to the unstimulated side. In **(B)** and **(D)**, the light gray squares represent the latency of saccade contralateral to the unstimulated side and the dark gray circles the latency contralateral to the cathode. The error bars correspond to one standard error of the mean (S.E.M.). Asterisks ($*p < 0.05$ and $**p < 0.01$) indicate main effects of saccade direction with respect to stimulation site **(D)** and the significantly different pairs revealed by a *post hoc* two-tailed *t*-test with Bonferroni correction.

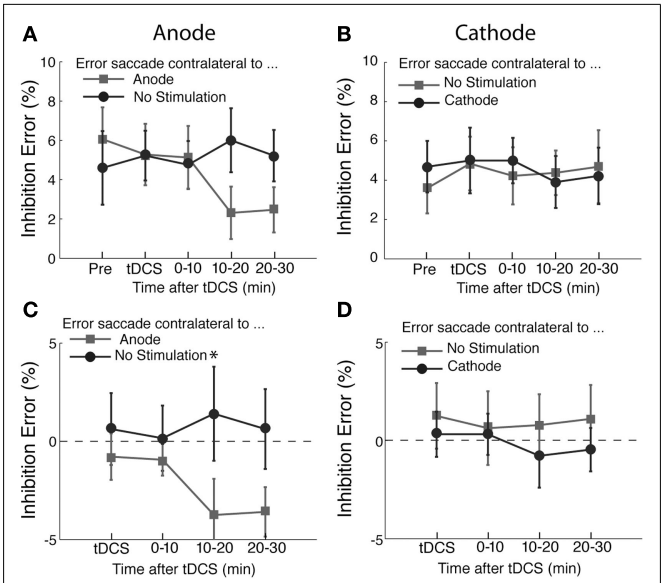

FIGURE 4 | Effects of tDCS on inhibition errors in the antisaccade task. The percentage of inhibition trials in which subjects made an error saccade toward the visual cue. In **(A)** and **(C)**, the light gray squares represent the percentage of errors of making saccade to the visual cue contralateral to the anode and the dark gray circles the percentage of error saccades to the visual cue contralateral to the unstimulated side. In **(C)**, the data shown in **(A)** was replotted after subtracting the pre-tDCS baseline to highlight changes induced by tDCS. In **(B)** and **(D)**, the changes of the error rates from the pre-stimulation blocks are shown in the same format as **(A)** and **(C)**. In **(D)**, the data shown in **(B)** was replotted after subtracting the pre-tDCS baseline to highlight changes induced by tDCS. The error bars correspond to one standard error of the mean (SEM). Asterisks ($*p < 0.05$ and $**p < 0.01$) indicate the significantly different pairs revealed by a post hoc two-tailed *t*-test with Bonferroni correction.

saccade direction, $F(1,45) < 1$; interaction, $F(3,45) < 1$) or saccade landing points (time course, $F(3,45) < 1$; saccade direction, $F(1,45) < 1$; interaction, $F(3,45) = 2.21$, $p = 0.09$).

INHIBITION ERRORS IN THE ANTISACCADE TASK AFTER tDCS

In order to evaluate possible changes in the ability to suppress automatic saccades toward the peripheral cue, we calculated the percentage of trials in which the subjects erroneously made a saccade to the peripheral cue and examined possible changes in the inhibition error rates due to tDCS.

The percentages of inhibition errors are shown in **Figure 4**. We found an effect of anodal tDCS as shown in **Figures 4A,C**. There was a significant interaction between the time course and saccade direction with respect to the stimulation site ($F(3,45) = 3.05$, $p < 0.05$). A *post hoc* test revealed that this interaction was due to a significant difference in the error rate during the period immediately after the delivery of tDCS ($T(15) = -2.35$, $p < 0.05$). There was no significant effect of time course ($F(3,45) < 1$) or saccade direction ($F(1,45) = 3.4$, $p = 0.08$). We did not find a significant effect of cathodal tDCS on the inhibition error rate (**Figures 4B,D**; Time course, $F(3,45) < 1$; saccade direction, $F(1,45) = 1.30$, $p = 0.27$; interaction, $F(3,45) < 1$).

DISCUSSION

In the present study, we have shown that tDCS over FEF can modulate saccade properties in prosaccade and antisaccade tasks. Our main findings are summarized as (1) anodal tDCS shortens the latency of contralateral prosaccades, (2) cathodal tDCS lengthens the latency of ipsilateral antisaccades, (3) anodal tDCS reduces automatic error saccade to the contralateral cue, and (4) saccade amplitudes and their variability are unaffected by tDCS. In this section, we elaborate on each of these points and provide comparisons with related TMS and lesion studies on FEF and saccade generation.

FACILITATION OF REFLEXIVE SACCADE BY ANODAL tDCS

The only effect we observed by tDCS over FEF in the prosaccade experiment was shortening of saccade latency in the direction contralateral to anodal stimulation. The positive effect of anodal tDCS and no effect of cathodal tDCS support the idea that the effect we found in the bilateral tDCS experiment is primarily due to the shortening of saccade latency due to activation of FEF by anodal stimulation rather than lengthening of latency due to suppression of FEF by cathodal stimulation.

Anodal tDCS is believed to increase the spontaneous firing rate of the cortex under the stimulating electrode by depolarizing the

membrane potential (Bindman et al., 1962; Creutzfeldt et al., 1962; Fregni and Pascual-Leone, 2007). Saccade latency is known to be dependent on the time when the firing rate of FEF reaches a threshold for saccade execution and the variability of saccade latency is due to the difference in the rate of increase in firing rate across trials (Hanes and Schall, 1996). In line with these findings, our results can be interpreted such that the firing rate in FEF reached the threshold for saccade execution more quickly due to the increased firing rate induced by anodal tDCS. Alternatively, our results are also compatible with the hypothesis that tDCS modulates the threshold for generating saccades and thereby shortening saccade latency. Further studies are needed to determine how tDCS influenced saccade latency. The shortening of the latency continued even up to 30 min after the tDCS delivery (**Figures 2A,D**). Since we measured the effect of tDCS only up to 30 min after the delivery of tDCS, it is unclear how long the effect lasts after anodal tDCS.

SLOWING OF IPISILATERAL ANTISACCADE BY CATHODAL tDCS

In the antisaccade task, cathodal tDCS delayed the generation of antisaccades toward the direction ipisilateral to the stimulation site. This is informative for understanding the functions of FEF and possibly the neighboring areas stimulated by tDCS in the antisaccade task. As we outlined in the introduction, FEF has been implicated in generation of volitional saccades and suppression of reflexive saccades. These two presumed functions of the FEF make distinct predictions as to the consequences of tDCS over FEF during the antisaccade task. If the generation of volitional saccades were to be suppressed by cathodal tDCS over FEF, the latency of contralateral saccades would have been prolonged. However, this is not clearly the case. Instead, the prolongation occurred only for ipisilateral saccades. This result may be regarded as somewhat puzzling, but can be understood if we assume that a successful antisaccade consists of a serial, rather than parallel, processes of suppression of an automatic reflexive saccade and programming and generation of a volitional saccade. In the ipisilateral antisaccade trials, the visual cue appeared on the side contralateral to the tDCS. If cathodal tDCS over FEF were to impair the suppression of reflexive saccade to the contralateral visual cue, it would take longer to suppress the reflexive saccade to the contralateral visual cue and thereby delay the programming of an ipisilateral saccade.

The finding of prolongation of ipisilateral antisaccade is consistent with previous TMS studies over FEF in the antisaccade task (Müri et al., 1991; Olk et al., 2006). In those studies, single pulse TMS was delivered over FEF either 50 ms before (Olk et al., 2006) or 50–90 ms after (Müri et al., 1991) the onset of a visual cue. In both cases, prolongation of the latency for ipisilateral saccades was found and no prolongation for contralateral antisaccades was found. These results suggest that both tDCS and TMS over FEF primarily interfere with suppression of reflexive saccades to the contralateral visual cue.

CHANGES IN INHIBITION ERRORS AFTER tDCS

A more direct way to test the idea that tDCS over FEF interferes with suppression of reflexive saccades is to examine the changes in the inhibition error rate after tDCS. If the cathodal tDCS over FEF impaired the ability to suppress reflexive saccades, the number of error saccades would be expected to increase. However, our results did not show a significant increase in the error rate (**Figure 4D**). It is possible that our experiment was not sensitive enough to detect a subtle change, because the typical rate of inhibition errors was about 5% of trials in our study and our estimates of the error rate were based on 40 saccades per condition for each subject. Therefore, one error saccade comprised 2.5% of trials and a small variability in the error rates would be very difficult to detect in the current study.

On the other hand, we did detect a small change in the inhibition error rate with the anodal tDCS, which produced a significant change. It reduced the errors of making saccades to the visual cue presented contralateral to the stimulation electrode. This is again consistent with the idea that tDCS over FEF modulates the suppression of reflexive saccades. That is, our results can be interpreted as anodal tDCS facilitated the FEF function to suppress erroneous reflexive saccades to contralateral visual cues.

LACK OF EFFECTS ON SACCADE AMPLITUDE AND VARIABILITY

Although anodal tDCS shortened the contralateral saccade latency, we did not find a change in accuracy as measured by the landing point and variability, which would be expected if one considered a potential trade-off between saccade latency and accuracy (Schall, 1995). A similar result was found in a TMS experiment in which TMS had an effect on latency but not accuracy (Priori et al., 1993). The antisaccade task is known to engage the FEF more than a prosaccade task (Connolly et al., 2002) and therefore it was expected that tDCS over FEF might produce a more pronounced effect on the saccade amplitude and variability. However, this was not observed. One possible reason for the lack of effects on saccade size is due to the fact that saccade target positions were always indicated by the hollow squares making the programming of saccade amplitude and directions robust to manipulations by tDCS.

COMPARISON OF tDCS EFFECTS BETWEEN THE PROSACCADE AND ANTISACCADE TASKS

So far, we have explained the effects of tDCS on prosaccades and antisaccade invoking a different mechanism for each. To explain the effect of cathodal tDCS in the antisaccade task, we assumed that cathodal tDCS impairs the suppression of contralateral reflexive saccade, and for the facilitation of prosaccades by anodal tDCS, we explained that prosaccade latency was shortened by enhanced activity level of FEF. These two explanations may appear to conflict with each other. The interpretation of the FEF activity as the efficiency of suppressing contralateral saccade contradicts the results of the prosaccade experiment. Conversely, if we interpret the FEF activity as the speed of saccadic response as we did for explaining the results of the prosaccade experiment, the results of the antisaccade experiment cannot be explained. For instance, the suppression hypothesis predicts that cathodal tDCS would shorten contralateral prosaccades by reducing the suppression of saccade generation. However, our results showed no effect, or if anything an opposite effect.

These apparent conflicts can be reconciled if we consider (1) that the effect of tDCS is dependent on the activity level during the task and (2) that FEF consists of both saccade execution neurons and saccade suppression neurons. In support of the first

point, an earlier study of tDCS showed that when tDCS was delivered over the motor cortex while subjects were engaged in a mental task, deactivating the motor cortex, subsequent effects of the tDCS on motor-evoked potentials were much reduced compared with delivery of tDCS during a passive condition (Antal et al., 2007). This suggests that neurons that are active during tDCS are more susceptible to the modulation by tDCS.

As for the second point, it is known that subset of FEF neurons with foveal receptive fields serve for suppressing saccade execution (Segraves and Goldberg, 1987) in a manner analogous to the rostral superior colliculus (Munoz and Wurtz, 1992, 1993). Moreover microstimulation of those neurons in FEF prolongs saccade latency in macaque monkeys (Burman and Bruce, 1997). Given the task dependency of tDCS, it is plausible that different subtypes of FEF neurons are affected between the prosaccade and antisaccade tasks. Specifically, in the prosaccade task, there is no task demand to suppress a reflexive saccade and therefore saccade execution neurons would be more active. On the other hand, saccade suppression neurons would be much more active during the antisaccade task. Therefore, it can be inferred that effects of tDCS was stronger for the saccade execution neurons in the prosaccade task, whereas it was stronger for the saccade suppression neurons in the antisaccade task. This framework provides explanations for the main two positive findings, namely, the effect of cathodal tDCS on antisaccades and the effect of anodal tDCS on prosaccades.

However, there remain two predictions made by this framework that are not measured in the present data. First, cathodal tDCS should have lengthened contralateral prosaccades. Second, anodal tDCS should have shortened ipsilateral antisaccade. As for the lack of these effects, it is possible that the effect size was too small to detect with our experimental procedures. In the unilateral cathodal tDCS condition, the prosaccade latency was slightly (∼3 ms) longer for the contralateral than ipsilateral saccades (**Figure 2F**). Since reflexive prosaccades are not heavily dependent on FEF (Pierrot-Deseilligny et al., 1991; Rivaud et al., 1994), suppression of FEF by cathodal tDCS may not be effective for increasing the latency. In the unilateral anodal tDCS condition, ipsilateral antisaccades were slightly (∼3 ms) longer, which is opposite to the prediction. However, the 3 ms differences were too small to reliably capture with the sampling rate of the eye tracker used in the present study (250 Hz); one frame corresponded to 4 ms, While the predictions mentioned here are not confirmed in our current experiments, those effects may be revealed with stronger stimulation protocols which may lead to a larger effect size.

PRACTICE EFFECT

One of the weaknesses of our present study is the lack of a sham condition, which introduces ambiguity as to whether latency change over time comes from effects of tDCS or practice over trials. While the unilateral tDCS conditions were used as a way to introduce a no stimulation condition, we cannot rule out the possibility that the FEF on the unstimulated side was modulated by tDCS over the contralateral FEF via interhemispheric connectivity between homologous regions (e.g., Suppa et al., 2008). In addition, there is a limitation in the comparison of the results of the unilateral tDCS conditions with the results of the bilateral tDCS experiment. Effects of tDCS tend to become weaker when extracephalic reference electrodes are used as in our unilateral tDCS conditions (Moliadze et al., 2010).

HEMISPHERIC ASYMMETRY OF FEF IN HUMANS

Hemispheric differences in the functions of human FEF have been reported in several aspects cognitive functions such as top-down attention to early visual areas (Silvanto et al., 2006; Ruff et al., 2009), conjunction search (Muggleton et al., 2003), and motor selection (Bardi et al., 2012). For example, the TMS over the left and right FEF exhibits different effects on visual areas. TMS over the left FEF increased the sensitivity of left MT/V5 (i.e., reduction of threshold for TMS-induced phosphenes in MT/V5), whereas the effect of TMS over the right FEF was observed in both left and right MT/V5 (Silvanto et al., 2006). A concurrent TMS-fMRI study showed that TMS over the left and right FEF both deactivates early visual areas corresponding to the central visual field, whereas activation of early visual areas representing visual periphery was specific to TMS over the right FEF (Ruff et al., 2009). These findings are compatible with the suggestion from clinical observations that the right FEF plays a more general attentional role covering both visual fields, whereas the role of the left FEF is more limited and restricted to contralateral visual field (Mesulam, 1981). Such hemispheric differences could potentially have added variability to our data. Further tDCS studies will be informative to further determine hemispheric differences in the function of the FEF.

COMPARISON OF tDCS AND TMS

The effects of anodal tDCS on prosaccade latency both in the bilateral and unilateral stimulation and the effects of cathodal tDCS in the antisaccade task both suggest that the induced electric current reached the FEF as intended. Further, as we have discussed, the effects of cathodal tDCS were by and large consistent with previous offline TMS studies on FEF both in the antisaccade tasks (Müri et al., 1991; Olk et al., 2006), again suggesting that the source of the effects is disruption of FEF.

One disadvantage of tDCS is that compared to TMS, the stimulation spreads to larger cortical regions due to the volume conduction (see, Wagner et al., 2006, 2007a,b) and it is more difficult to ensure the intended target cortical area is stimulated. A study of tDCS over the motor cortex showed that effectiveness of tDCS depends the position of the reference electrode (Nitsche and Paulus, 2000) because the direction of current flow with respect to the cortical surface is critical for excitability change by tDCS (Landau et al., 1964). The optimal electrode montage for FEF stimulation therefore remains to be determined. To obtain larger effects in future studies, it is important to consider the possibility that different electrode montages may induce greater effects.

One of the advantages of tDCS over TMS for interfering with FEF functions is that tDCS does not produce uncomfortable twitches or eye blinks. Also, the auditory and tactile sensations produced by a TMS pulse briefly suppress the generation of microsaccades for a few hundred milliseconds (Kanai et al., 2008). Such an artifact would potentially be a serious concern in oculomotor studies.

CONCLUSION

In summary, our present study shows that tDCS can be used to modulate activity of FEF over a time course of up to 30 min. It opens the possibility of applying tDCS for studying functions of FEF and for enhancing oculomotor and attentional performance in the future.

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Altering automatic verbal processes with transcranial direct current stimulation

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Background: Word retrieval during verbal fluency tasks invokes both automatic and controlled cognitive processes. A distinction has been made between the generation of words clusters and switches between such clusters on verbal fluency tasks. Clusters, defined by the reporting of contiguous words that constitute semantic or phonemic subcategories, are thought to reflect relatively automatic processing. In contrast, switching from one subcategory to another is thought to require a more controlled, effortful form of cognitive processing. **Objective:** In this single-blind, sham-controlled experiment, we investigated whether anodal and cathodal transcranial direct current stimulation (tDCS) can differentially modify controlled or automatic processes that support lexical retrieval, as assessed by clustering and switching on verbal fluency tasks, in 24 healthy right-handed adults. **Methods:** Participants were randomly assigned to receive 1 mA of either anodal (excitatory) or cathodal (inhibitory) active tDCS over the left dorsolateral prefrontal cortex in addition to sham stimulation over the same region in counterbalanced order. Participants engaged in various cognitive activities during the first 23 min of stimulation. Then, during the final segment of each 30-min session, they completed letter- and category-cued word fluency tasks. **Results:** Participants reported more words on category-cued word fluency tasks during anodal than sham stimulation (25.9 vs. 23.0 words; $p = 0.055$). They also showed a net increase in the number of clustered words during anodal stimulation compared to a net decrease during cathodal stimulation (1.3 vs. −1.5 words; $p = 0.038$). **Conclusion:** tDCS can selectively alter automatic aspects of speeded lexical retrieval in a polarity-dependent fashion during a category-guided fluency task.

Keywords: verbal fluency, clustering, switching, transcranial direct current stimulation

INTRODUCTION

Overt behaviors are often generated by a variable admixture of automatic and controlled processes. Verbal fluency tasks have been widely used to assess these processes governing lexical retrieval in healthy adults and various patient populations for both research and clinical purposes. During verbal fluency tasks, it has been hypothesized that internal or external cues activate chains of automatic associations, resulting in the successive generation of related words (i.e., "clustering," as in the contiguous generation of the words shirt, socks, skirt, and shoes on a letter-cued fluency task using the letter "s"). When these automatic associations dissipate, then effortful cognitive control processes are used to find new cues, thereby initiating another automatic chain (i.e., "switching," as is seen when one goes from providing exemplars of farm animals to providing exemplars of zoo animals on an category-cued fluency task with the category "animals"). The operations of these two distinct processes, automatic and controlled, are thought to be reflected in the nature of the items produced, and in the time of production: automatic processes give rise to clusters of related items with relatively short inter-item intervals, while controlled processes lead to switches among subcategories after longer intervals.

For verbal fluency tasks, there is evidence that automatic processes are associated with the dominant (left) posterior temporal-parietal regions, while controlled processes are associated with the dominant (left) prefrontal region (Hirshorn and Thompson-Schill, 2006). Different verbal fluency tasks likely invoke varying combinations of automatic or controlled processes, and hence different weightings of anatomic dependence. Letter fluency tasks have been associated with greater activation of the left frontal lobe (as assessed by functional magnetic resonance imaging, fMRI), whereas category fluency tasks activate left temporal regions to a greater extent (Birn et al., 2010).

Clustering and switching processes are modulated by a number of participant characteristics. Evidence suggests that older healthy adults switch less frequently on category-cued fluency tasks and produce larger clusters on letter-cued fluency tasks than younger adults (Troyer et al., 1997). Alzheimer disease and focal lesions of

the left temporal lobe are associated with the production of smaller clusters than are typically produced by healthy age-matched controls (Troyer et al., 1998). Conversely, patients with Parkinson's disease and multiple sclerosis appear to switch less frequently than both healthy controls and some patient populations, although their clustering remains intact (Troster et al., 1998).

Transcranial direct current stimulation (tDCS) involves passing weak direct electrical current through the intact scalp to alter the functioning of underlying cerebral tissues. A rapidly growing body of evidences demonstrates that tDCS can induce changes in physical and cognitive functioning (Stagg and Nitsche, 2011). Stimulation with tDCS is thought to produce a relatively localized, polarity-dependent alteration of the electrical potential of the cortical tissue beneath the scalp electrode. The effects of these alterations can be excitatory with the application of anodal stimulation, or inhibitory with the application of cathodal stimulation. As tDCS is typically applied, 1–2 mA of direct current is administered via 25–35 cm^2 saline-soaked sponges for up to 40 min. Under these conditions, the technique has been found to be safe and unobtrusive (Iyer et al., 2005). Depending on the duration of stimulation and the experimental situation, some effects of tDCS can persist for minutes, hours, days, or even more than a week (Reis et al., 2009). The ability of tDCS to activate or inhibit brain function over short and long time intervals and the fact that active stimulation can be counterbalanced with sham stimulation make tDCS an attractive tool for investigating and perhaps enhancing cognitive processes.

Initial investigations of tDCS as a means of modifying cognitive functioning have shown some promise in improving implicit learning of a motor sequence, probabilistic learning, memory consolidation, and working memory, among other skills (Miniussi et al., 2008). A few studies have found that anodal stimulation can improve selected aspects of language functioning in healthy adults. For example, tDCS has been shown to improve language learning (Floel et al., 2008) and facilitate implicit learning of an artificial grammar in healthy adults (de Vries et al., 2010). Further, anodal tDCS applied to the left frontal lobe has been found to shorten picture naming latencies among healthy adults in several studies (e.g., Sparing et al., 2008). A fMRI study found that decreased naming latencies following tDCS were associated with decreased blood oxygen level-dependent signal in the left inferior frontal cortex (Holland et al., 2011). Some tDCS-related improvements in picture naming accuracy have also been documented in persons with post-stroke aphasia (e.g., Baker et al., 2010). On verbal fluency tasks, Iyer et al. (2005) found that anodal tDCS applied to the left prefrontal cortex produced modest, though significant, increases in the total number of words produced on a letter fluency task in healthy adults. Cattaneo et al. (2011) also found a facilitative effect of anodal tDCS relative to sham on overall productivity during letter- and category-cuedword fluency tasks during anodal stimulation of Broca's area in healthy adults.

Here we sought to extend prior findings and further investigate the ability of tDCS to modify the automatic and controlled aspects of speeded verbal production among healthy adults. Based on prior neuroimaging and stimulation studies, we hypothesized that anodal and cathodal tDCS applied over the left prefrontal cortex would enhance and impede, respectively, verbal fluency production. We also hypothesized that stimulating the left prefrontal cortex would produce greater polarity-dependent effects on letter-cued than category-cued fluency, as well as greater effects on controlled (i.e., switching) than automatic (i.e., clustering) word retrieval processes.

MATERIALS AND METHODS

PARTICIPANTS

Forty adults were recruited from the Johns Hopkins University via word-of-mouth and from the Baltimore metropolitan area using Craigslist. All participants were healthy, right handed (as assessed by the Edinburgh Inventory), native English speakers. All participants also completed at least 12 years of schooling ($M = 14.6$ years, SD = 2.3) and were of at least average estimated intelligence ($M = 104.2$, SD = 8.0) based on the Hopkins Adult Reading Test (HART; Schretlen et al., 2009). This study was approved by the Johns Hopkins Medicine Institutional Review Board, and all participants provided written informed consent.

During the random assignment of participants to the anodal/sham or cathodal/sham condition, younger and more highly educated adults were markedly over-represented in the anodal group. Consequently, we conducted a secondary series of exploratory analyses after better equating the two experimental conditions with respect to age and educational attainment. Specifically, we excluded subjects as necessary, starting with the youngest participants from the anodal/sham group and the least educated participants from the cathodal/sham group, in order to form two equal-sized groups that were matched for age, education, and estimated intelligence (all $ps > 0.05$). Through this process we retained a final sample of 24 adults, aged 24–55 years ($M = 35.7$; SD = 10.1). Characteristics of the final sample of study participants are shown in **Table 1**.

PROCEDURES

In this single-blind experiment, subjects were assigned to receive one 30-min session of either anodal (facilitative) or cathodal (inhibitory) active tDCS together with 30 min of sham stimulation using a random number sequence. Active and sham stimulation were administered in counterbalanced order and separated by a 90-min washout period.

Stimulation was applied via a constant current stimulator (Iomed Phoresor II Model PM850) using two saline-soaked sponge electrodes (5.2 cm × 5.2 cm). The active electrode was placed over the left prefrontal region (F3 according to the 10-20 International EEG positioning system), and the reference electrode was placed over the vertex (Cz). In the active stimulation conditions, current was ramped up to 1.0 mA over 30 s and remained at 1 mA for the remainder of the 30-min session. Consistent with prior research, current in the sham stimulation condition was ramped up to 1.0 mA and then covertly ramped back down to 0 mA over 60 s, thereby habituating participants to the sensations (e.g., warmth, tingling) of tDCS (Nitsche et al., 2008).

Because maximal gains usually are achieved when tDCS is coupled with behavioral training (Reis et al., 2009), participants spent the first 24 min of each stimulation session engaging in expressive language tasks such as object naming and oral reading. The activities and stimuli were identical in the active and sham conditions.

Table 1 | Characteristics of study participants by experimental condition.

Characteristic	Experimental condition[1]		Statistic	*p*-Value
	Anodal ($N = 12$)	Cathodal ($N = 12$)		
Sex, male/female	6/6	5/7	$X^2_{(1)} = 0.17$	0.68
Age[2] (years)	37.9 ± 11.3	33.5 ± 8.7	$t_{(22)} = 1.08$	0.29
Education[2] (years)	14.8 ± 2.0	15.3 ± 2.9	$t_{(22)} = -0.41$	0.69
Estimated IQ[2]	104.7 ± 7.5	103.5 ± 10.3	$t_{(22)} = 0.33$	0.74

[1]*Anodal = active anodal plus sham stimulation. Cathodal = active cathodal plus sham stimulation.*

[2]*Values expressed as mean ± standard deviation.*

During the last 6 min of each 30-min session, participants completed four 60-s verbal fluency tasks: for letter-cued trials, they were asked to report as many words as possible beginning with the letters "s" and "p." For the category-cued trials they were asked to report as many animals and supermarket items as possible. Both were drawn from the Calibrated Ideational Fluency Assessment (CIFA; Schretlen and Vannorsdall, 2010). Responses were recorded using a studio-quality microphone and Audacity (version 1.2.6) software. Verbal fluency productions were transcribed and scored offline.

Verbal fluency protocols were scored following the Hopkins qualitative verbal fluency system (Ledoux et al., 2009), which is a modification of the criteria developed by Troyer et al. (1997). The system uses specified criteria to determine the total number of acceptable words generated, numbers of switches and clusters, mean cluster size, and percent words in clusters for both letter-cued and category-cued verbal fluency tasks. All scoring was conducted by trained research assistants who were blind to the participant stimulation condition.

ANALYSES

In the full sample ($n = 40$), multivariate ANCOVAs adjusting for participant age and education were used to test for differences in fluency output by condition (anodal vs. cathodal) and to compare active (anodal or cathodal) vs. sham stimulation. We also assessed difference scores in verbal fluency productions during anodal and sham stimulation (i.e., anodal minus sham) relative to the difference scores during cathodal and sham stimulation (i.e., cathodal minus sham).

After equating the groups for age and education, our sample size ($n = 24$) was not suitable for a multivariate ANCOVA. We therefore examined the distribution of each dependent variable and conducted between-groups comparisons of verbal fluency output by the anodal and cathodal stimulation groups using independent samples *t*-tests (for normally distributed variables) and the Wilcoxon signed-ranks test (for variables with non-normal distributions). Within-groups analyses were used to compare fluency during active (anodal or cathodal) vs. sham stimulation using paired *t*-tests. Independent samples *t*-tests or Wilcoxon signed-ranks tests were also used to assess difference scores in verbal fluency productions during anodal and sham stimulation (i.e., anodal minus sham) relative to the difference scores during cathodal and sham stimulation (i.e., cathodal minus sham).

RESULTS

For the sample as a whole, multivariate ANCOVAs revealed no significant within- or between-groups effects of tDCS on any of the verbal fluency variables with respect to either letter- or category-cued fluency tasks ($ps \geq 0.25$).

In the subsample of participants in which groups were well matched with respect to potential confounders, there were no significant effects of tDCS on overall letter-cued fluency productivity ($ps > 0.05$). Similarly, for letter-cued fluency there were no significant between-groups (anodal vs. cathodal) or within-groups (active vs. sham) effects of stimulation on any of the qualitative fluency measures ($ps > 0.05$).

With respect to possible effects of anodal and cathodal stimulation on category-cued verbal fluency, the overall productivity of the two groups did not differ significantly and there were no differences in qualitative aspects of verbal fluency between the groups ($p > 0.05$).

When we examined the distributions of dependent variables, two (percent words in clusters during active anodal stimulation and percent words in clusters during sham anodal stimulation) violated the assumption of normality, whereas the others did not. Analyses revealed a trend toward greater category-cued verbal fluency productivity during active anodal relative to sham stimulation [active $M = 25.9$, SD = 6.2; sham $M = 23.0$, SD = 5.6; $t(11) = 2.14$, $p = 0.055$]. Active anodal stimulation was also associated with the production of more words in clusters relative to sham stimulation [active $M = 22.1$, SD = 7.5; sham $M = 18.3$, SD = 8.1; $t(11) = 2.41$, $p = 0.035$]. During active anodal tDCS, participants also showed a trend toward reporting a greater percentage of words in clusters relative to sham tDCS (active Median = 87.3, Interquartile range = 15.1; sham Median = 78.4, Interquartile range = 14.9; $Z = -1.88$; $p = 0.06$). No differences between active and sham tDCS were found for the number of switches or mean cluster size ($ps > 0.05$).

We next compared differences in the number of word clusters participants produced during active than sham stimulation as a function of current polarity. Compared to sham stimulation, participants showed a net increase in word clusters during active anodal stimulation ($M = 1.3$, SD = 2.5), whereas they showed a net decrease in word clusters during active cathodal stimulation ($M = -1.5$, SD = 3.6). This difference was significant, $t(22) = -2.21$; $p = 0.038$ and is depicted in **Figure 1**. Similarly, compared to sham stimulation, active anodal tDCS led to a 6.6%

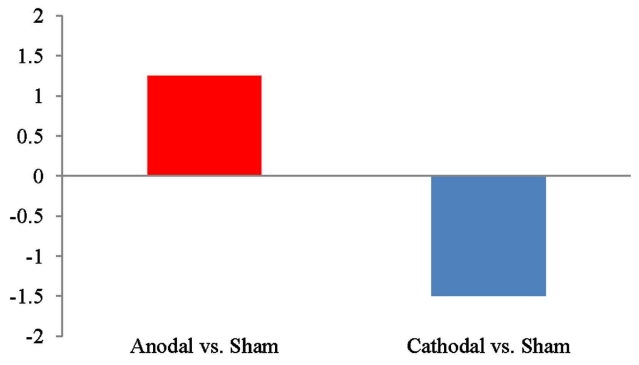

FIGURE 1 | Effects of active stimulation conditions compared to sham stimulation with respect to the numbers of words in clusters during a category-cued fluency task.

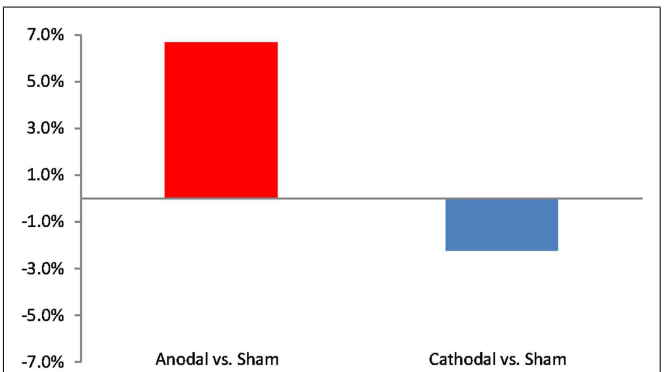

FIGURE 2 | Effects of active stimulation conditions compared to sham stimulation with respect to the percent words in clusters during a category-cued fluency task.

increase in the percent of words in clusters, whereas active cathodal stimulation produced a 2.2% reduction in the percent words in clusters. This difference [$t(22) = -2.12$, $p = 0.046$] is shown in **Figure 2**. There were no significant effects of tDCS on switching or mean cluster size ($ps > 0.05$).

DISCUSSION

We hypothesized that active anodal and cathodal tDCS would, respectively, enhance and diminish overall productivity on tests of verbal fluency. Based on our placement of the active electrode over the left dorsolateral prefrontal cortex, we expected to find more prominent tDCS effects on letter- than category-cued tasks and on measures of controlled (i.e., switching) than automatic (i.e., clustering) word retrieval processes. In a subsample of participants matched for basic demographic characteristics, our results provide partial support for our hypotheses in that anodal tDCS selectively enhanced aspects of verbal fluency while cathodal stimulation inhibited the same processes. However, our predictions regarding the type of fluency task and the qualitative aspects of fluency performance that would be most affected by tDCS were not supported.

In fact, we found that active anodal tDCS affected category-cued fluency productivity but had no discernible effects on letter-cued verbal fluency. Nor did tDCS alter controlled cognitive aspects of word retrieval (i.e., switching), despite our application of stimulation over the left dorsolateral prefrontal cortex, an area often associated with executive functioning and set-shifting. Rather, we found a nearly three-word increase in productivity on category-cued verbal fluency tasks in the anodal stimulation condition relative to the sham condition. Analyses of the qualitative aspects of verbal fluency productions suggest that this enhanced productivity was likely due to the increased clustering seen with anodal stimulation relative to both the sham and cathodal stimulation, and not due to changes in switching. Although more modest in its effect, cathodal stimulation also reduced clustering relative to sham stimulation.

The fact that we found effects of tDCS exclusively for category fluency, and not letter fluency, differs from the two other studies of tDCS and verbal fluency in healthy adults. Iyer et al. (2005) found facilitative effects of 2 mA of anodal tDCS on overall productivity on a test of letter-cued fluency compared to sham and cathodal conditions. However, they did not find effects of tDCS in their initial experiment which used a lower current intensity (1 mA) and participants in their study did not complete category-cued fluency tasks. Cattaneo et al. (2011) also used 2 mA of anodal stimulation and found improved productivity for both letter and category-cued fluency relative to sham stimulation. Although group means are not presented, a figural representation of the data suggests a larger magnitude of effect for category-cued relative to letter-cued fluency. Thus, our lack of findings for letter-cued fluency may be due to our decision to use 1 mA rather than 2 mA of current. We chose to use 1 mA because pilot testing revealed that subjects could reliably detect active stimulation at 2 mA whereas they could not at 1 mA. Thus, in our effort to blind our study participants to the stimulation condition, we may have also reduced the effectiveness of the experimental intervention. In addition, we administered sham and active tDCS separated by a 90-min washout during each session. We based this decision on evidence that the cortical excitability effects of short duration tDCS typically return to baseline by 60–90 min after the cessation of stimulation (Nitsche and Paulus, 2001). However, if active tDCS stimulation combined with directed cognitive activity produces longer-last effects, this could have limited our ability to detect the behavioral effects of active tDCS. Future studies should explore whether increasing administration of a greater current density would produce effects for letter-cued fluency, as well as whether administering stimulation to more posterior regions would produce effects on both types of word fluency tasks.

Another weakness of this study is the heterogeneity of the initial study sample and unbalanced randomization into study groups. Participants were recruited through two methods, flyers placed on the Johns Hopkins University and medical campuses and through Internet ads (i.e., Craigslist). As a result, we recruited a rather homogenous group of young, well-educated participants along with a larger group of individuals having more diverse demographic characteristics. When examining the effects

of tDCS on verbal fluency, we found no effects of tDCS within the full sample of participants. One hypothesis for this lack of findings is that the healthy, young, highly educated individuals who were over-represented in the anodal condition were already performing at ceiling and masked the effects of tDCS within the remaining participants. In fact, when the sample was trimmed to form two groups matched for relevant characteristics only then were the effects of tDCS apparent. Future studies should further explore the role of patient characteristics in relation to participant responsiveness to experimental interventions.

A related limitation to the current study is that, due to the small size of the final sample, we were unable to use multivariate ANOVA. Nor did we adjust for multiple comparisons. The latter decision was based on the fact that this was an exploratory study that aimed to determine whether tDCS could selectively alter controlled and automatic aspects of verbal fluency productions in healthy adults. We believe that the present findings, while relatively weak, suggest that tDCS can alter these word retrieval processes, as well as overall productivity on such tasks.

A final weakness is that this study employed a single-blind rather than double-blind experimental design. The tDCS device we used is not programmable in a way that permits one to blind both the experimenter and participant to the experimental condition. We did have one experimenter administer the cognitive testing while another operated the tDCS device, but this did not blind the machine operator to the experimental condition, and the other experimenter usually could discern whether a recipient was receiving active or sham stimulation. A procedural "workaround" for this limitation is possible but cumbersome in practice, and was not used in the present study. Fully programmable tDCS devices that overcome this limitation are recommended for use in future studies.

To our knowledge, this is the first study to investigate the utility of tDCS as a means of altering automatic and controlled aspects of speeded lexical during both letter and category word fluency tasks in neurologically healthy adults. We found that anodal tDCS was associated with an increase in overall productivity during a category-guided verbal fluency task, and that anodal stimulation led to a relative increase in clustering whereas cathodal stimulation had the opposite effect. These findings, although preliminary, suggest that tDCS may be an effective tool in ameliorating language dysfunction in disorders characterized by deficient activation or functioning of the semantic network. Our ongoing work is exploring this issue in such individuals including those with aphasia, autism spectrum disorders, and schizophrenia.

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Learning, memory, and transcranial direct current stimulation

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Transcranial direct current stimulation (tDCS) has been the subject of many studies concerning its possible cognitive effects. One of the proposed mechanisms of action for neuromodulatory techniques, such as transcranial magnetic stimulation and tDCS is induction of long-term potentiation (LTP) and long-term depression (LTD)-like phenomena. LTP and LTD are also among the most important neurobiological processes involved in memory and learning. This fact has led to an immediate interest in the study of possible effects of tDCS on memory consolidation, retrieval, or learning of various tasks. This review analyses published articles describing beneficial or disruptive effects of tDCS on memory and learning in normal subjects. The most likely mechanisms underlying these effects are discussed.

Keywords: tDCS, memory, learning

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are rapidly emerging as potential neuromodulatory tools; TMS already has approved therapeutic applications in neurology and psychiatry (Ragert et al., 2008; Celnik et al., 2009; Hummel et al., 2009; Brunoni et al., 2010).

The after-effects of both rTMS and tDCS sessions are believed to be related to long-term depression (LTD) and long-term potentiation (LTP)-like phenomena (Lømo, 2003; Esser et al., 2006), as well as to induction of gene expression and other mechanisms (Fritsch et al., 2010). During tDCS protocols, a weak current (1 or 2 mA) is delivered by a battery through a pair of electrodes attached to the scalp. In the case of anodal tDCS, the anode is attached to the scalp area to be stimulated and the cathode to the contralateral supraorbital area on the forehead; the arrangement is reversed for cathodal tDCS. It is well established that anodal tDCS increases cortical excitability whereas cathodal tDCS increases the excitability threshold probed with single transcranial magnetic pulses over the motor cortex (Jacobson et al., 2012). Anodal tDCS has been found to depolarize neuronal membranes, while cathodal tDCS induces hyperpolarization. Both carbamazepine, a sodium channel blocker, and flunarizine, a calcium channel blocker, have been found to preclude these effects. Moreover, long-lasting excitability after-effects in either direction can be blocked by dextrometorphane, an *N*-methyl-D-aspartate (NMDA) receptor antagonist (Nitsche et al., 2003).

Studies with rTMS are far more numerous than those with tDCS, but the latter technique is gradually gaining more attention, especially due to its potential advantages: it is less expensive, more portable, and allows for very effective sham stimulation in experimental protocols (Gandiga et al., 2006).

A drug or procedure capable of improving memory in both normal individuals and patients is sort of a "Holy Grail" in medicine. Since LTD and LTP are also strongly involved in memory and learning, a logical hypothesis would be that both rTMS and tDCS would be capable of either disrupting or improving these processes in normal subjects and patients. This possibility has led to the recent publication of many experimental results of neuromodulation of memory and learning processes in both normal subjects and patients.

In this review we will discuss experimental work dealing with potential neuromodulatory effects of tDCS upon learning and memory in normal subjects. It is important to understand how tDCS may affect the normal brain before attempting to use it therapeutically. A clear advantage of tDCS over rTMS in this setting is that it provides a truly sham stimulation to be compared to actual cortical stimulation (with TMS, even especially designed "sham coils" do not evoke the same scalp sensations as real stimulation). tDCS does not evoke any scalp sensations apart from an initial itching while current is being adjusted; this may be replicated by a few seconds of electrical stimulation followed by current interruption during sham sessions. This effectively rules out placebo effects, arousal, enhancement of attention and other non-specific actions of the tDCS procedure (Sparing and Mottaghy, 2008).

EFFECTS ON LEARNING

One of the earliest and most interesting studies of the effects of tDCS upon memory consolidation and retrieval took advantage of the ease of application and unobtrusiveness of the technique and applied anodal tDCS bilaterally over frontocortical sites every 30 min during sleep periods rich in slow-wave activity, resulting in subsequent improvement in tests of declarative memory (Marshall et al., 2004).

The effect of prefrontal cortex tDCS on implicit learning was also tested in the setting of a probabilistic classification learning (PCL) protocol (Kincses et al., 2004). Ten minutes of anodal tDCS applied to the left prefrontal cortex of 22 healthy subjects while

they performed a PCL task improved implicit learning; in contrast, no effect was observed with either cathodal left prefrontal stimulation or primary visual cortex tDCS.

In order to investigate the role of the primary motor cortex (M1) in motor learning, especially in the formation of motor memories, Galea and Celnik (2009) applied anodal tDCS to M1 of nine healthy subjects during motor training. Anodal tDCS was found to increase the magnitude and duration of motor memories.

In another learning paradigm, namely implicit learning of an artificial language, de Vries et al. (2010) found that after 20 min of tDCS applied to Broca's area during the acquisition of an artificial grammar, subjects performed better in a violation detection task than controls who had undergone sham stimulation or real tDCS to another brain area unrelated to speech.

Another cortical area, the posterior parietal cortex (PPC), has been studied during anodal tDCS in several visual orienting tasks (Bolognini et al., 2010). It has been found that right PPC anodal tDCS, but not left PPC anodal tDCS, enhances visual search skills when applied either by itself or in addition to training.

EFFECTS ON WORKING MEMORY

During a verbal n-back working memory (WM) task, as n (i.e., WM load) increases, subjects show poorer behavioral performance. A brief period of practice or even increased familiarity with the task can improve WM performance and lead to activation changes in the PPC in neuroimaging studies. Parietal tDCS was shown to be capable of hampering the improvement in performance, giving further support to the role of the PPC in this kind of task (Sandrini et al., 2012).

On the other hand, Fregni et al. (2005) reported that, on a three-back WM task, 15 normal subjects had significant accuracy improvement in the task during anodal tDCS of the left prefrontal cortex; this could not be explained by slowed responses, since response times were not changed by stimulation. Moreover, cathodal tDCS of the same area or anodal stimulation of the primary motor cortex (M1) had no effect. The authors concluded that left prefrontal anodal stimulation leads to enhancement of WM performance. Their results were later confirmed by other investigators (Ohn et al., 2008; Andrews et al., 2011).

The neurophysiological basis for modulation of WM by left dorsolateral prefrontal cortex was investigated with recording of underlying electroencephalographic activity (Zaehle et al., 2011).

After anodal tDCS, oscillatory power in the theta and alpha bands was amplified and WM performance enhanced; on the other hand, cathodal tDCS decreased alpha and theta oscillatory activity and disrupted WM.

The effect of transcranial random noise stimulation (tRN) of the left dorsolateral prefrontal cortex on a WM task was compared to the effects of tDCS applied to the same region (Mulquiney et al., 2011). While tDCS increased the speed of performance of the two-back WM task, tRN had no effect.

The first study to verify whether left anodal tDCS applied to the DLPC (dorsolateral prefrontal cortex, corresponding to the F3 position of the 10–20 international system for EEG electrode placement) during the persistent performance of a WM task would improve performance on a subsequent WM task to a greater extent that either previous tDCS at rest or cognitive activity by itself was performed by Andrews et al. (2011). The result was that the combination of anodal tDCS applied to the DLPC with a WM task was superior to either tDCS or the cognitive task alone in improving the performance of a subsequent digit span forward task.

Although left prefrontal anodal stimulation increased accuracy without changing response times, bifrontal tDCS has been found to slow reaction times in a WM task (Marshall et al., 2005). More specifically, anodal and cathodal tDCS were applied bilaterally over prefrontal regions, over 15 min repeatedly (15-s-on/15-s-off), while subjects performed a modified Sternberg task. There were also sham tDCS sessions. Under such experimental conditions, reaction times increased linearly with set size, and the slope of such increase was comparable for active and sham stimulation; this was regarded as evidence that the time required for memory scanning had not been affected by tDCS. However, reaction times were slowed during active stimulation as compared to sham tDCS, indicating that real stimulation had impaired neuronal processing related to response selection and preparation.

In contrast to these findings, another series of experiments (Ferrucci et al., 2008) reported no increase in accuracy by bilateral prefrontal tDCS and faster reaction times after cathodal bilateral tDCS of the prefrontal cortices during a modified Sternberg task. The authors explain the discrepancy between their results and those previously described in the literature on the basis of differences in tDCS methodology. In fact, Ferrucci et al. used a non-cephalic reference electrode; there were also differences in wash-out periods and in intensity of stimulation. In addition, however, Ferrucci et al. also tested the effect of cerebellar tDCS during performance of the modified Sternberg test, finding that such stimulation impaired the usual practice-dependent proficiency increase.

The finding that patients with parietal lobe damage may exhibit selective WM impairment in recognition but not in recall tasks was the basis for a study in which normal subjects underwent cathodal (i.e., inhibitory) tDCS to the right inferior PPC and then performed separate blocks of an object WM task probed by recall or recognition. WM was selectively impaired in recognition tasks, as is usually the case for patients with parietal lesions (Berryhill et al., 2010).

EFFECTS ON MEMORY RETRIEVAL

The role of the temporal lobes on the generation of false memories was investigated by Boggio et al. (2009). Thirty normal subjects underwent one of three stimulating conditions during the acquisition and retrieval phases: anodal left/cathodal right anterior temporal lobe tDCS, left anodal anterior temporal lobe tDCS and sham tDCS stimulation. Both forms of active stimulation resulted in a decrease of 73% in the formation of false memories, without any effect on the veridical ones.

The reports of enhanced visual memory in autism, together with left hemisphere deficit and right hemisphere compensation, led to a study in which normal subjects who had left cathodal (i.e., inhibitory) anterior frontal tDCS in conjunction with right anodal (i.e., excitatory) anterior frontal tDCS showed an improvement in visual memory similar to that described for autistics (Chi et al., 2010).

Fronto-temporal tDCS has been used to probe the specific role of each cerebral hemisphere on the enhancement of memories

with different emotional valences (Penolazzi et al., 2010). Right anodal/left cathodal tDCS was found to specifically enhance the recall of pleasant images with respect to both unpleasant or neutral images; conversely, left anodal/right cathodal tDCS favored the recall of unpleasant images over pleasant or neutral ones. This result was interpreted as supportive of the specific-valence hypothesis, which holds that the right cerebral hemisphere specializes in processing of unpleasant memories, while the left hemisphere specializes in the processing of pleasant memories (Penolazzi et al., 2010). Such result, however, is somewhat puzzling, since in most tDCS paradigms anodal stimulation, being excitatory, has been found to improve function (Jacobson et al., 2012), but in this case one would have to interpret its effect as detrimental to the stimulated cortical area in order not to contradict the specific-valence hypothesis. The authors hypothesize, therefore, that excessive stimulation of the underlying fronto-temporal cortex could result in impairment of processing of unpleasant memories in the right hemisphere or of the pleasant ones in the left hemisphere (Penolazzi et al., 2010).

DISCUSSION

Most tDCS studies performed so far show a consistent positive effect of left DLPC anodal stimulation on WM, when the cathode is applied to the right supraorbital region. This effect may not occur, or even be reversed, with different electrode montages, such as bilateral prefrontal stimulation (Marshall et al., 2005) or use of a non-cephalic cathode (Ferrucci et al., 2008).

Anodal stimulation of cortical areas specifically engaged in learning the task at hand also seem to enhance performance, as in the case of Broca's area during language tasks (de Vries et al., 2010), the PPC in visual orientation tasks (Bolognini et al., 2010), the primary motor cortex during motor learning tasks (Galea and Celnik, 2009), the prefrontal cortex during implicit learning (Kincses et al., 2004), or even the left DLPC during a persistent WM task (Andrews et al., 2011).

Inhibitory (i.e., cathodal) tDCS has been investigated regarding its ability to disrupt normal cortical physiology. Particularly noteworthy are studies attempting to induce "reversible lesions." This was the case for the study of cathodal tDCS of the PPC, which resulted in selective WM impairment for recognition tasks (Berryhill et al., 2010) and of both temporal lobes, which reduced the formation of false memories (Boggio et al., 2009). A "savant-like" phenomenon was also induced by frontal inhibitory (i.e., cathodic) stimulation, which resulted in improved visual memory (Chi et al., 2010). However, as recently pointed out in a meta-analytical review of the effects of tDCS polarity in the motor and cognitive domains (Jacobson et al., 2012), it is often difficult to generate cathodal inhibitory effects in cognitive studies.

A noteworthy study which is also not in line with the overall impression that anodic stimulation usually improves function of the underlying cortical area is the one dealing with emotional enhancement of memories (Penolazzi et al., 2010). In order not to contradict the specific-valence hypothesis, one would have to assume, as did the authors of that manuscript, that in their specific paradigm anodal stimulation of the left hemisphere impaired processing of pleasant memories instead of facilitating it. Further studies should therefore be undertaken in order to accept or refuse such assumption.

CONCLUSION

Although there are still few studies of the effects of tDCS upon normal physiologic processes underlying learning and memory, most results are remarkably consistent with the experimental hypothesis of a major role for the left DLPC in WM, and also show that WM performance can be enhanced by anodal stimulation over this area. By the same token, anodic stimulation of Broca's area, the primary motor cortex and other areas primarily involved in specific learning paradigms can also enhance performance. Moreover, there seems to be a summation of the effects of tDCS and training (Andrews et al., 2011); this might well be of therapeutic value in the near future. tDCS has also been proven capable of inducing "reversible lesions" of specific cortical areas, which are useful for disclosing the normal interplay of excitation and inhibition between different cortical areas during learning and memory processes.

Further studies are required to shed light into the intrinsic mechanisms of such effects (Gladwin et al., 2012). Cathodal inhibitory effects, in particular, have not been obtained in many cognitive studies and the reasons for this are still poorly understood (Jacobson et al., 2012). The association of tDCS with neuroimaging studies would be interesting to ascertain that areas under anodic influence are actually stimulated and that those under the cathode are inhibited in different experimental paradigms; TMS could also be used to probe changes in intracortical inhibition and facilitation in response to tDCS. The development of uniform stimulation protocols is also important to allow for direct comparison between studies (Teo et al., 2011).

In the future, after further understanding of its mechanisms of action is obtained and optimal stimulation protocols are developed, tDCS may become a valuable strategy to improve learning in both normal subjects and patients.

Finally, we believe that experiments should be devised to establish how stable these effects are, since beneficial effects on learning and memory will be much more meaningful if they are found to be durable or even permanent.

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Parietal contributions to visual working memory depend on task difficulty

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The nature of parietal contributions to working memory (WM) remain poorly understood but of considerable interest. We previously reported that posterior parietal damage selectively impaired WM probed by recognition (Berryhill and Olson, 2008a). Recent studies provided support using a neuromodulatory technique, transcranial direct current stimulation (tDCS) applied to the right parietal cortex (P4). These studies confirmed parietal involvement in WM because parietal tDCS altered WM performance: anodal current tDCS improved performance in a change detection task, and cathodal current tDCS impaired performance on a sequential presentation task. Here, we tested whether these complementary results were due to different degrees of parietal involvement as a function of WM task demands, WM task difficulty, and/or participants' WM capacity. In Experiment 1, we applied cathodal and anodal tDCS to the right parietal cortex and tested participants on both previously used WM tasks. We observed an interaction between tDCS (anodal, cathodal), WM task difficulty, and participants' WM capacity. When the WM task was difficult, parietal stimulation (anodal *or* cathodal) improved WM performance selectively in participants with high WM capacity. In the low WM capacity group, parietal stimulation (anodal *or* cathodal) impaired WM performance. These nearly equal and opposite effects were only observed when the WM task was challenging, as in the change detection task. Experiment 2 probed the interplay of WM task difficulty and WM capacity in a parametric manner by varying set size in the WM change detection task. Here, the effect of parietal stimulation (anodal or cathodal) on the high WM capacity group followed a linear function as WM task difficulty increased with set size. The low WM capacity participants were largely unaffected by tDCS. These findings provide evidence that parietal involvement in WM performance depends on both WM capacity and WM task demands. We discuss these findings in terms of alternative WM strategies employed by low and high WM capacity individuals. We speculate that low WM capacity individuals do not recruit the posterior parietal lobe for WM tasks as efficiently as high WM capacity individuals. Consequently, tDCS provides greater benefit to individuals with high WM capacity.

Keywords: tDCS, PPC, working memory, task difficulty, individual differences

INTRODUCTION

Keeping a running subtotal as we shop, remembering a new acquaintance's name for a subsequent introduction, maintaining the distance of the car behind us as we switch lanes – these are examples of daily activities that rely on working memory (WM). WM serves as our mental workspace and as such it plays an essential role in cognition. Given this central role, cognitive researchers have devoted considerable efforts developing and refining theoretical models of WM (for reviews see Baddeley and Hitch, 1974; Cowan, 1993; Baddeley, 2000; Miyake et al., 2001; Oberauer, 2002; Curtis and D'Esposito, 2003; Cowan et al., 2005; Chein and Fiez, 2010). More recent work has focused on extending cognitive models to identify the neural correlates of WM, including the contributions of the inferior and superior parietal lobes comprising posterior parietal cortex (PPC; for reviews see Jonides et al., 1993; Cohen et al., 1997; Courtney et al., 1997; Ungerleider et al., 1998; Chein and Fiez, 2001; Munk et al., 2002; Pessoa et al., 2002; Linden et al., 2003; Sala et al., 2003; Olson and Berryhill, 2009; Brady et al., 2011). WM studies commonly identify PPC activations in functional magnetic resonance imaging (fMRI), yet only recently have these activations been functionally associated with WM rather than attention (Wager and Smith, 2003; Todd and Marois, 2004, 2005; Song and Jiang, 2006; Xu and Chun, 2006; Xu, 2007, 2009). Notably, activity in the intraparietal sulcus parametrically increases according to the number of items maintained in WM according to an individual's WM capacity limit (Todd and Marois, 2004, 2005). These fMRI data point toward parietal involvement in WM maintenance, but converging evidence from neuropsychological patients is only partly consistent with this view. We found that patients with bilateral parietal damage were selectively impaired at blocks of WM trials probed by old/new recognition but not recall (Berryhill and Olson, 2008b). Yet, when recall and recognition WM trials were intermingled making the retrieval demands unpredictable these same patient

participants could perform normally on recognition WM trials (Berryhill et al., 2011). Our conclusion was that under certain conditions the patients with bilateral parietal damage uniformly applied a recall strategy (e.g., in the unpredictable rather than the blocked WM task). We interpreted these data as indicative of PPC involvement in the strategic attentional refreshing of items in WM that were not subject to active verbal rehearsal (Berryhill et al., 2011). An important prediction that this view promotes is that when verbal rehearsal strategies are limited, the PPC is needed for accurate WM performance.

One complementary approach to the neuropsychological and neuroimaging described above is neuromodulatory. Here, we used transcranial direct current stimulation (tDCS) during which small amounts of electric current are applied to the scalp to modulate the excitability of underlying neural populations (Nitsche and Paulus, 2000; Rosenkranz et al., 2000; Antal et al., 2004a; Paulus, 2011; Stagg and Nitsche, 2011; Jacobson et al., 2012). This is an appealing alternative because it can modulate the activity in relatively small regions of cortex without the influence of cortical reorganization as may happen with patients. In addition, a within-subjects design can be implemented. In tDCS the direction of current flow is determined by the placement of the anodal (+) and cathodal (−) electrode. Although it is a simplification, anodal tDCS has been associated with the depolarization of neurons and making them more likely to fire whereas cathodal tDCS has been associated with hyperpolarizing neurons and making them less likely to fire (Purpura and McMurtry, 1965). Although the mechanism of tDCS remains an area of active research, there is evidence to suggest that in the cortex tDCS modulates synaptic strength and likely stimulates pyramidal neurons and interneurons (Nitsche et al., 2005; Stagg and Nitsche, 2011). As a therapy, tDCS has shown some success in treating major depression (Fregni et al., 2006a,b; Brunoni et al., 2011), memory deficits in Parkinson's disease (Boggio et al., 2006), memory deficits in Alzheimer's disease (Boggio et al., 2009, 2011, 2012), aphasia (Baker et al., 2010; Kang et al., 2011; You et al., 2011), and as a recovery aid for stroke patients (Fregni et al., 2005b; Miniussi et al., 2008; Jo et al., 2009; Kang et al., 2009; Bolognini et al., 2011; Bueno et al., 2011). Despite these findings, less research has been done investigating the effects of tDCS on WM.

Several studies have used tDCS to investigate verbal WM. In these studies researchers have applied anodal tDCS to the left prefrontal cortex with the consistent finding that stimulation improved verbal WM performance using 2- and 3-back WM tasks (Fregni et al., 2005a; Ohn et al., 2008; Andrews et al., 2011; Mulquiney et al., 2011; Zaehle et al., 2011). These results also showed that cathodal stimulation of the left prefrontal cortex did not improve accuracy on the task. However, changes in cognitive abilities have not been tested with neuromodulation as thoroughly as with motor functions and in patient populations. Studies of tDCS in cognitive domains find a variable pattern of results and do not always match the predicted anodal-excitatory, cathodal-inhibitory effect (Jacobson et al., 2012).

Only two WM-tDCS studies that we know of have stimulated cortical regions other than the left prefrontal cortex. First, Berryhill et al. (2010) used tDCS to study PPC contributions to visual WM tested by recognition or recall. Healthy young adults who received cathodal tDCS to the right PPC (P4) were selectively impaired when making WM recognition judgments but performance on recall tasks remained intact (Berryhill et al., 2010). Anodal tDCS did not impair recognition WM. However, recently a second group found that *anodal* tDCS applied to the right PPC improved WM in a change detection WM recognition task, but cathodal tDCS had no effect on WM (Tseng et al., 2012, personal communication). In short, both studies found evidence for right PPC involvement in WM, specifically visual WM tested by recognition; however, the type of stimulation and the consequences of stimulation were inconsistent. There were several important differences between the studies that might have explained the different tDCS effects. First, there were important paradigmatic differences. The two WM tasks tested were quite different and they varied in task difficulty as well. The required amount of sustained attention and number of items was different between tasks. Another important difference between experiments was the difference in participants' WM capacity, which was not measured in either of the previous studies. In this study, we report a different effect of tDCS depending on individual WM capacity. We reasoned that differential tDCS effects might be due to increased reliance on the PPC accompanying increases in task difficulty. However, this was only part of the story. To preview our results, tDCS applied to the PPC leads to different WM effects depending on WM task demand, but a second important factor is an individual's WM capacity.

MATERIALS AND METHODS

EXPERIMENT 1: PPC INVOLVEMENT IN VISUAL WM

The purpose of Experiment 1 was to determine the role of the right PPC in visual WM tasks. We directly compared performance in two previously tested WM recognition tasks (Berryhill et al., 2010; Tseng et al., 2012) that had confirmed functional PPC involvement in recognition WM but with inconsistent findings. In the first case (Berryhill et al., 2010), cathodal tDCS impaired WM performance and in the second case, anodal tDCS to the right PPC improved WM performance (Tseng et al., 2012, personal communication). Here, participants performed both WM tasks in a within-subjects design. A perfect replication of each of the previous findings would have required a complex pattern of results. Namely, anodal tDCS to the right PPC was expected to benefit the change detection WM task, but not the sequential WM task and cathodal tDCS to the right PPC was expected to disrupt the sequential WM task but not the change detection task. Although this prediction is based on the previous findings it struck us as unparsimonious because it required a tDCS (cathodal, anodal) by task (change detection, sequential presentation) crossover interaction. We thought it would be more likely that anodal or cathodal tDCS to the PPC would have uniform effects on WM performance in both tasks. For example, anodal stimulation should improve performance on both tasks or cathodal stimulation should inhibit performance on both tasks. This would be the case unless other task related factors were mediating the role of the PPC.

Participants

Twenty neurologically normal right-handed young adults (average age 23.25, SD 3.46, 12 females) participated. No participants were under the effects of neuroleptic, hypnotic, or seizure medications.

No participant had a history of significant neurological or psychiatric disease or significant head injuries. All procedures were conducted in accordance with the University of Nevada Institutional Review Board. Participants were compensated $15/hour.

TDCS protocol

As in Berryhill et al. (2010) and Tseng et al. (2012), there were three tDCS testing sessions: anodal, cathodal, and sham (control condition). Sham stimulation incorporates 20 s of stimulation during the ramping up phase as in the actual stimulation conditions, however, after the 20 s stimulation ends. This has been shown to be an effective method for keeping participants blind to the condition (Gandiga et al., 2006). Conditions were administered on different days during 30-min testing sessions counterbalanced across participants. In all conditions one electrode was placed over the right parietal cortex at P4 (International 10-20 EEG system). The reference electrode was placed on the contra lateral cheek (Berryhill et al., 2010). In the anodal condition the anode was over P4 and in the cathodal condition the cathode was over P4. P4 was selected because it was used in both of the previously described PPC studies and would lead to closer replication of the methods used. P4 also was shown to influence WM recognition in previous studies. In the sham condition either the anode or cathode was placed over P4 in counterbalanced order. The order of stimulation conditions was counterbalanced across participants. Participants often took part in the study in consecutive days, however some gaps were longer. The gaps between sessions did not extend beyond a week between sessions. No participants reported any side effects which is consistent with other tDCS studies (Kessler et al., 2012).

Stimulation consisted of a single continuous direct current delivered by a battery-driven continuous stimulator (Eldith MagStim, GmbH, Ilmenau, Germany). Current was delivered through two 5 cm × 7 cm electrodes housed in saline-soaked sponges. During cathodal and anodal stimulation 1.5 mA current was applied for 10 min. Previous studies have found an effect of tDCS with 10 min of stimulation (Furubayashi et al., 2008; Berryhill et al., 2010; Andrews et al., 2011; Mulquiney et al., 2011; Antal et al., 2012; Berryhill and Jones, 2012; Kasashima et al., 2012). During sham stimulation participants received stimulation in which current lasted for 20 s at the start and end of the 10 min but no stimulation occurred in between. This gives participants the experience of feeling a minor tingling at most to have the appearance of stimulation. During stimulation participants performed practice trials of both procedures as to become familiar with each task. Immediately following the 10 min the electrodes were removed and the researchers left the room so that the participant could perform the task. Both experimental procedures were programmed using ePrime 2.0 (PST, Pittsburgh, USA). The experiment was conducted on Dell Optiplex 980 computer and stimuli were presented on a Dell 24″ monitor which participants sat 57 cm from. The University of Nevada Reno IRB approved all protocols.

Experimental tasks

Sequential presentation task. Here, six visual stimuli were presented sequentially at fixation (1000 ms each; Berryhill and Olson, 2008a; Berryhill et al., 2010). The visual stimuli consisted of 72 colorized drawings of common objects (e.g., frog, arm; Rossion and Pourtois, 2004). The stimuli were approximately 20° × 10° of visual angle and they were presented on a uniform white background. A checkerboard mask (1000 ms) appeared after the sixth stimulus and then a seventh test stimulus appeared (until response). The test stimulus was one of the previous six 50% of the time (old) and a new stimulus 50% of the time (new). Participants made a new/old button response to indicate if the seventh test item was one of the first six (**Figure 1**).

Change detection task. The change detection WM task was similar to that used by Tseng et al. (2012). Each trial began with a central fixation cross (1000 ms). Next, eight randomly colored squares (3° × 3° of visual angle) appeared simultaneously at

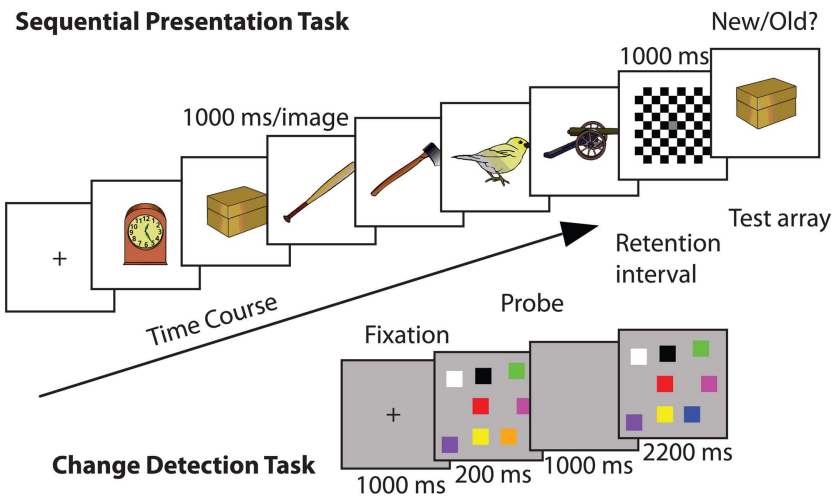

FIGURE 1 | Example trials of each of the WM tasks used in Experiment 1: (top) sequential presentation WM task: in each trial a series of images were presented and after a delay a probe image appeared: (bottom) change detection WM task in which a visual array was presented and after a delay a probe image appeared. In both cases the response was to report whether the probe image was old or new.

random locations presented against a medium gray background (200 ms), followed by a retention interval (1000 ms). The colored squares were equiluminant with the exception of black and white. The RGB values were as follows: yellow (255, 255, 0), white (255, 255, 255), teal (0, 210, 255), red (255, 0, 0), purple (156, 0, 255), pink (255, 0, 255), orange (255, 168, 0), green (0, 255, 0), blue (0, 0, 255), black (0, 0, 0), and aqua (0, 255, 216). The colored squares were created in Adobe Photoshop and only the hue changed between the squares. The luminance level remained the same. At test, the stimulus display reappeared (2200 ms) and participants had to make an old/new response indicating whether a single square had changed color (50% trials). The background color differences between the trial types helped to inform the participants of which type of trial would be next (**Figure 1**).

Digit span. We also administered tests of forward and backward digit WM span to each participant before the sham stimulation session. For each participant a combined score (forward span + backward span) was calculated as a measure of WM span. The digit span task is a useful measure of cognitive abilities. The digit span task is frequently used to measure cognitive capabilities (Parkinson et al., 1980; Conklin et al., 2000; Pisoni and Geers, 2000; Lefebvre et al., 2005).

Analysis

Here, we report the data using normalized difference indices (tDCS − sham/tDCS + sham) to minimize between-subject variability. Difference indices were used to normalize the effect of stimulation for each participant. These values were compared using a mixed model repeated measures ANOVA with the within-subject factors of task (sequential presentation, change detection) and tDCS condition (anodal, cathodal) and the between-subjects factor of WM span (high, low). Several other measures of WM performance accuracy were calculated [raw accuracy, corrected recognition (CR), WM capacity (Cowan's K), and discrimination (d')] with consistent findings across measures. All analyses were subject to Bonferroni correction.

Results

To demonstrate that there was no effect of tDCS unless WM capacity was considered, we conducted a repeated measures ANOVA including the within-subjects factors of WM task (sequential presentation, change detection) and the two stimulation difference indices (anodal, cathodal). As expected, there were no main effects of task or stimulation condition and no significant interactions (all p's > 0.50). We anticipated this result, as this analysis failed to adequately account for the pattern in the data because it did not include a cognitive measure of WM capacity. We divided the participants into two groups based on their WM capacity. High and low WM capacity groups were defined by a median split on the combined forward and backward WM digit span scores. The high and low WM capacity groups had significantly different combined digit span scores (M low = 10.80 SD = 1.14, M high = 14.10 SD = 0.74, $t_{18} = 7.71$, $p < 0.001$). The forward digit span scores had a range of 5–9 and the backward digit span scores had a range of 4–7.

A second repeated measures ANOVA on the difference indices of accuracy including the between-subjects factor of group found that there were no main effects of stimulation condition ($F_{1,18} = 0.096$, $p = 0.760$, partial $\eta^2 = 0.005$), or WM task ($F_{1,18} = 0.553$, $p = 0.467$, partial $\eta^2 = 0.030$). The main effect of WM capacity group was significant ($F_{1,18} = 5.685$, $p = 0.028$, partial $\eta^2 = 0.240$), such that the high WM capacity group received a benefit of tDCS and the low capacity group was impaired by tDCS; see **Figure 2**. Importantly, the interaction of WM capacity group and WM task was significant ($F_{1,18} = 9.648$, $p = 0.006$, partial $\eta^2 = 0.349$). The high WM capacity group received a global tDCS benefit and the low WM capacity group was globally impaired by tDCS, but this difference only emerged in the change detection task. To characterize the difficulty differences between the two tasks we compared performance in both tasks with d' using a paired-samples t-test and found that performance on the sequential presentation task was significantly better than performance on the change detection task (d' mean: sequential presentation task: 2.88, SD = 0.67,

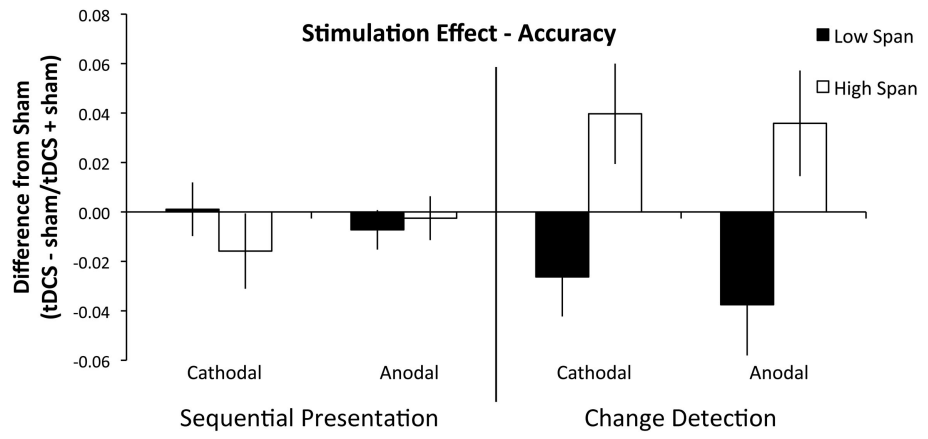

FIGURE 2 | Experiment 1 results. Performance is plotted as a difference index using performance accuracy values (tDCS − sham/tDCS + sham). Values above 0 indicate superior performance in the tDCS condition; values below 0 indicate impaired performance after tDCS. The sequential task is presented on the left and the change detection task on the right. The low WM span group is plotted in black and the high WM span group is plotted in white. Error bars represent the SEM. There was a significant between-group effect of tDCS across stimulation condition and WM task.

change detection task: 0.81, SD = 0.10, $t_{19} = 10.58$, $p < 0.001$, $r^2 = 0.85$).

To investigate further, we conducted two independent samples t-tests on the difference indices of accuracy on the change detection task between WM capacity groups and found that the anodal (high WM capacity mean difference index = +3.6, low WM capacity mean difference index = −3.8: $t_{18} = 2.612$, $p = 0.018$, $r^2 = 0.13$) and cathodal (high WM capacity mean difference index = +3.9, low WM capacity mean difference index = −2.6: $t_{18} = 2.694$, $p = 0.015$, $r^2 = 0.29$) effect between WM capacity groups was significant. No other interactions approached significance (all p's > 0.384). We also conducted two independent samples t-test on the sequential presentation task between WM capacity groups and found that the anodal (high WM capacity mean difference = −0.003, low WM capacity mean difference = −0.007: $t_{18} = 0.954$, $p = 0.353$, $r^2 = 0.05$) and cathodal (high WM capacity mean difference = +0.021, low WM capacity mean difference = +0.001: $t_{18} = 0.418$, $p = 0.681$, $r^2 = 0.01$) effect between WM capacity groups was not significant (**Table 1**).

Discussion

Experiment 1 showed that the parietal contributions to WM may be quite different depending on participant's WM capacity. High and low WM capacity groups responded in nearly equal and opposite directions to parietal tDCS. This finding replicated Tseng et al.'s report of anodal improvement of WM performance. However we only observed this effect *in the high WM capacity group*. We also observed improved WM performance after cathodal tDCS to the right PPC in the high WM capacity group. The Berryhill et al. data were also partially replicated, but only in the low WM capacity group, and only in the change detection WM task. In short, these data partially replicated Berryhill et al. (2010) and Tseng et al. (2012). Previous tDCS studies targeting parietal cortex reported a similar effect of anodal and cathodal stimulation. Here, WM performance in the high WM capacity group improved after either anodal and cathodal tDCS whereas performance in the low WM capacity group was impaired. Furthermore, the effect of tDCS on the change detection task performance was significantly greater than the effect on performance in the sequential presentation task.

In Experiment 1 there were significant differences in the two WM tasks. Neither the high nor low WM capacity group experienced a significant effect of tDCS on the sequential presentation task. This task was significantly easier and slower paced than the change detection task and it raises the possibility that the PPC was not recruited equally in each task. Additionally, in the sequential presentation task there may have been alternative strategies (e.g., verbal rehearsal of items) that activated other cortical regions to compensate for altered PPC function. A verbal rehearsal strategy would be impossible in the change detection task because of the fast presentation rate and the difficult-to-name aspect of the spatial configurations. However, performance on the change detection task was modulated by tDCS and WM capacity. The high WM capacity group benefited from anodal *and* cathodal tDCS suggesting that the PPC was differentially contributing to WM performance in low and high WM capacity groups.

EXPERIMENT 2: MODULATING TASK DIFFICULTY IN WM CHANGE DETECTION

There were several limitations in Experiment 1. First, there was a notable inter-task difficulty differential: the change detection task was significantly more difficult than the sequential presentation task. Second, high and low WM capacity individuals showed nearly equal and opposite effects of right PPC stimulation. Consequently, in Experiment 1 it was impossible to determine whether differences in WM performance were due to WM task demands or WM capacity. Experiment 2 addressed these confounds. We parametrically modulated task difficulty by varying the set size in the change detection WM task. We predicted that PPC involvement would increase with WM load as seen in previous fMRI research (Todd and Marois, 2004, 2005; Song and Jiang, 2006; Xu and Chun, 2006) and supported by our findings from Experiment 1. If the results in Experiment 1 were due to task difficulty, increasing WM task difficulty should place greater demands on relevant cortical structures such as the PPC and result in linear effects and improved WM performance.

Participants

Twenty-eight neurologically normal right-handed young adults (mean age 22.29, SD 3.05, 24 females) participated. Seven participants had also participated in Experiment 1. We conducted the same median split from Experiment 1 on the combined digit span scores for all participants. This allowed us to create a high WM capacity (mean = 14.07, SD = 1.59) and low WM capacity group

Table 1 | Mean accuracy scores (SD) for all participants (total), the high WM capacity group (H), and the low WM capacity group (L).

	Sham			Anodal			Cathodal		
	Total	**H**	**L**	**Total**	**H**	**L**	**Total**	**H**	**L**
E1. Sequential Presentation	91 (0.05)	90 (0.04)	91 (0.06)	90 (0.06)	90 (0.05)	90 (0.06)	90 (0.08)	88 (0.07)	92 (0.09)
E1. Change Detection	63 (0.07)	63 (0.08)	64 (0.07)	64 (0.10)	68 (0.08)	60 (0.10)	64 (0.08)	68 (0.08)	61 (0.06)
E2. Set Size 4	82 (0.06)	84 (0.02)	82 (0.01)	83 (0.07)	84 (0.02)	81 (0.02)	81 (0.08)	83 (0.02)	79 (0.02)
E2. Set Size 6	69 (0.06)	70 (0.02)	68 (0.02)	71 (0.06)	73 (0.02)	69 (0.01)	69 (0.07)	70 (0.03)	68 (0.01)
E2. Set Size 8	62 (0.05)	62 (0.02)	62 (0.01)	66 (0.06)	68 (0.01)	64 (0.02)	65 (0.07)	67 (0.01)	63 (0.02)

Rows 1 and 2 represent the tasks from Experiment 1 (E1) and rows 3–5 represent the set sizes in Experiment 2 (E2).

(mean = 10.42, SD = 0.76). The range for the forward digit span was from 5 to 9 and the range of the backward digit span was 3–9.

Methods

Experiment 2 repeated the tDCS protocol and the change detection WM task described in Experiment 1 with one change. Additional set sizes (4, 6, and 8) were included to parametrically vary task difficulty. There were 100 trials of each set size pseudo randomly interleaved for a total of 300 trials. Anodal, cathodal, and sham conditions were used in a counterbalanced order across participants. The experimental task lasted ∼20 min.

Results

As in Experiment 1, high and low WM capacity groups were defined by performing a median split on their combined forward and backward digit span scores. A repeated measures ANOVA was conducted analyzing the within-group factors of stimulation (anodal, cathodal), and set size (4, 6, and 8) and the between-group factors of WM capacity group (high, low). There was a main effect of stimulation condition ($F_{1, 26} = 5.060$, $p = 0.033$, partial $\eta^2 = 0.163$) such that anodal stimulation (**Figure 3**) benefited WM performance more than cathodal stimulation (**Figure 4**). There was also a main effect of set size ($F_{2, 52} = 4.375$, $p = 0.018$, partial $\eta^2 = 0.144$) such that tDCS effects followed a significant linear trend ($p = 0.008$, partial $\eta^2 = 0.240$). Specifically, as set size increased, the effect of stimulation also increased. The within-subject contrast analysis on high WM capacity difference scores showed a linear trend for both anodal ($p = 0.030$, partial $\eta^2 = 0.314$) and cathodal stimulation ($p = 0.037$, partial $\eta^2 = 0.294$). It is possible that the cathodal effect in the high WM capacity group could best be explained by an exponential fit. However, paired-samples t-test indicated that there was no significant difference between mean r^2 values as expressed by a linear ($M = 0.534$) versus exponential ($M = 0.527$) trend ($t_{13} = 0.120$, n.s.) Finally, the between-subject effect of group reached significance ($F_{1, 26} = 5.097$, $p = 0.033$, partial $\eta^2 = 0.164$). The high WM capacity group showed a performance improvement following stimulation. Stimulation had a negligible effect on performance for the low WM capacity group. We conducted additional one-sample t-tests comparing the difference indices of the high WM capacity group from zero, or no change. The difference scores for the set size of 8 were significant for both the anodal ($t_{13} = 3.303$, $p = 0.006$, $r^2 = 0.46$) and cathodal stimulation ($t_{13} = 2.725$, $p = 0.017$, $r^2 = 0.36$). Pairwise comparisons of the 4 and 6 set size values were not significant (all t-values > 0.083). The same comparisons for the low WM capacity group were conducted and no measures reached significance. The cathodal difference score for a set size of four was the closest to significance ($t_{13} = 1.802$, $p = 0.095$, $r^2 = 0.20$). None of the interactions reached significance (all p's > 0.268).

Discussion

In Experiment 2, we investigated the role that task difficulty plays in PPC involvement in WM task performance. This experiment

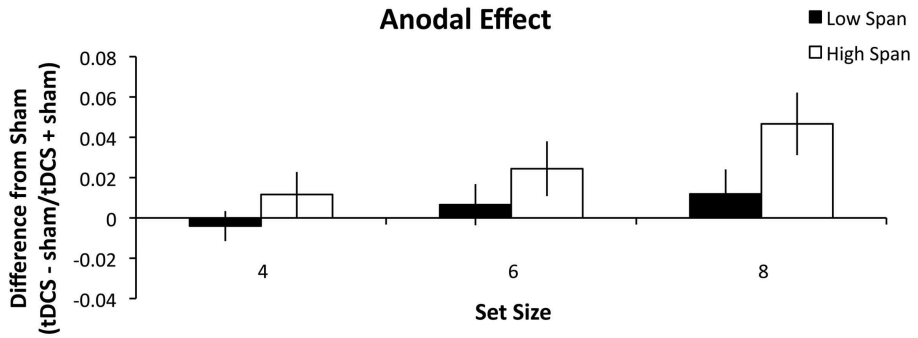

FIGURE 3 | Experiment 2 results. The difference indices for anodal tDCS on WM accuracy. Error bars represent the SEM.

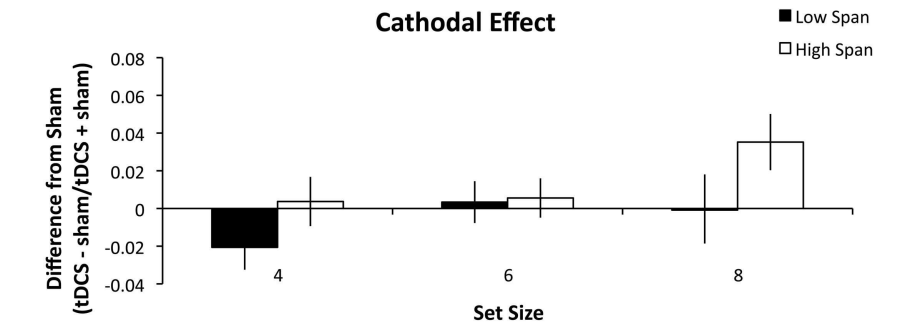

FIGURE 4 | Experiment 2 results. The difference indices for cathodal tDCS on WM accuracy. Error bars represent the SEM.

eliminated the task by difficulty confound in Experiment 1 by parametrically modulating set size to create three different levels of difficulty. Following Experiment 1, we predicted that the high WM capacity participants would benefit from tDCS and that the low WM capacity group would be impaired. We found that the high WM capacity group again benefited from either anodal or cathodal tDCS and that this benefit increased as task difficulty increased. However, here, the low WM capacity group was largely unaffected by tDCS except the decrease in performance seen following cathodal stimulation in the set size 4 condition. The increased benefit seen in performance following stimulation as difficulty increases reflects the strain put on the PPC by the task demands. This leads us to conclude that the PPC is needed more for recognition tasks that are more demanding than for those that are not. This is in support with previous research showing that PPC activity is greater with increasing WM loads (Todd and Marois, 2004; Song and Jiang, 2006).

GENERAL DISCUSSION

Here we confirmed PPC involvement in WM using tDCS. In Experiment 1, we compared the effects of anodal and cathodal P4 tDCS on two different WM tasks: sequential presentation and change detection. Stimulation effects were greater in the change detection task. We also found that the direction of the tDCS effects depended on participants' WM capacity. The low WM capacity group's performance was generally impaired by tDCS whereas the high WM capacity group's performance improved. Again, it was important to demonstrate that ignoring important group differences would obscure significant findings. Future research using tDCS should take this into account, as small sample sizes are common in tDCS studies making between-groups analyses under powered. In Experiment 2, we found that tDCS effects increased with WM task difficulty. As in Experiment 1, there were group differences. The high WM capacity group benefited from tDCS, and this effect was strongest in the anodal tDCS condition. Accordingly, we concluded that PPC involvement is greater in more difficult WM recognition tasks. These findings serve to resolve some of the discrepancy in the WM-tDCS literature by showing that tDCS to functionally involved regions can either improve or impair performance. The implications of these findings are discussed below.

PPC involvement in visual WM

The current findings are consistent with an interpretation we previously espoused called the *internal attention* model (Berryhill et al., 2011). Briefly, PPC contributions to WM can be described as strategically attending to items in WM and refreshing their representations. Accordingly, PPC involvement was predicted when the memoranda were difficult to verbalize, when attentional switching was compromised by a dual task paradigm, and when a passive WM strategy was adopted. This last prediction is thought to be associated with WM trials probed by recognition because participants may not engage an active verbal rehearsal strategy that is thought to draw more heavily on prefrontal involvement. The present WM paradigms probed WM using recognition. Yet, differential effects of PPC stimulation were noted in Experiment 1. This observation is consistent with our previous predictions because the change detection task met several of the criteria of the internal attention hypothesis: the stimuli were difficult to rehearse, making a deliberate verbal rehearsal strategy difficult. The change detection task may therefore be more reliant on attentional refreshing than the sequential presentation task. Furthermore, the slow pace of the sequential presentation task may not strain attentional resources as heavily as the faster-paced change detection task.

Previous research has shown that anodal tDCS to the right PPC, but not the left PPC, improves visual search and attentional skills (Bolognini et al., 2010). This was shown by improving visual search performance after tDCS and task training. The visual search findings help to explain our results as well. In the current study, anodal tDCS may not have only boosted attentional resources in the PPC allowing for better performance, but it also may have made visual processing more efficient. It is also possible that participants varied their strategy in the sequential presentation task and sometimes performed an active rehearsal strategy and other times relied on attentional refreshing. Averaging WM performance across trials would also show a smaller effect of tDCS than what was observed in the change detection task. Another factor that we previously predicted would increase PPC involvement was task difficulty. This prediction was born out in Experiment 2. We conclude that these data are consistent with a role for the PPC in the attentional refreshing process.

Group differences modulate tDCS effect size

Perhaps the most interesting finding here were the differences in the effect of tDCS to the PPC on low and high WM capacity groups. The high WM capacity group revealed a greater benefit of tDCS across WM tasks and stimulation condition. However, the low WM capacity group did not see a uniform stimulation effect across both experiments. In Experiment 1 the low WM capacity group was uniformly impaired by tDCS. This pattern of nearly equal and opposite effects in high and low WM capacity groups may explain why previous groups have had difficulty identifying any effect of tDCS. In Experiment 2, there was no effect of tDCS in the low WM capacity group. Previously we reported that less educated older adults did not benefit from frontal lobe tDCS but better educated adults benefited (Berryhill and Jones, 2012). Experiment 2 replicated the finding that high WM capacity predicted a larger benefit of tDCS whereas low WM capacity showed no improvement. We suspect that the differences in digit span score and education level both are reflecting the same underlying mechanism. To our knowledge there are only two other studies incorporating measures of group differences. In one case a motor learning task showed that the effect of tDCS to the motor cortex varied according to a participant's genotype for brain-derived neurotrophic factor (BDNF; Cheeran et al., 2008). In the second, in an emotional stimulus categorization task, tDCS to the dorsolateral prefrontal cortex had a greater effect on introverts than extraverts (Pena-Gomez et al., 2011). Future studies will be needed to identify the relevant factors influencing the magnitude of tDCS effects.

Other researchers have found important differences in WM strategy across individuals with different WM capacities (e.g., Cokely et al., 2006; Imbo and Vandierendonck, 2007; Bailey et al., 2008; Baldwin and Reagan, 2009; Unsworth and Spillers, 2010). Low WM span individuals are less able to ignore distracters

(Unsworth, 2007), rely on context to recall items, and have fewer attentional resources (Conway and Engle, 1996; Kane et al., 2001; Unsworth and Spillers, 2010). Recent research has shown that high WM capacity participants adopted more efficient strategies in a category naming task compared to low WM capacity participants (Schelble et al., 2012). Importantly, however, when instructed to use the same strategy as the high WM capacity participants the low WM capacity participants performed just as well. This suggests that it is not a fundamental inability but rather a miscalculation that can be remedied through training. Another recent WM study found that participants used different strategies based on the demands of the WM task (Sandrini et al., 2012). In a series of *n*-back tasks, participants employed different strategies for 1-back, when compared to 2- or 3-back tasks. These authors conclude that the 1-back tasks can rely on stimulus familiarity because the task is to identify repetitions whereas 2- or 3-back tasks may require recollection to overcome the presence of intervening stimuli. Further research is underway to examine whether the differences we observed can be explained by differences in WM strategy. Particularly given the safety and affordability of tDCS, it will be important to define with some confidence who, when, and how individuals will benefit from tDCS.

Mechanisms of tDCS

Apart from WM strategy, tDCS may have different effects on participants because of differences in their biology (morphological and genetic), which remain poorly understood. Animal research involving tDCS found that anodal tDCS increased neuronal activity and cathodal tDCS decreased neuronal activity (Purpura and McMurtry, 1965). However, within deeper layers of cortex, the opposite effect was seen such that anodal stimulation deactivated neurons and cathodal stimulation activated them. This suggested that neuronal orientation is important to understanding the effect of tDCS (Purpura and McMurtry, 1965). Within the cortex, tDCS modulates synaptic strength and likely stimulates neurons in the cortex, pyramidal neurons, and interneurons (Stagg and Nitsche, 2011). Several neuromodulators such as GABA (Stagg et al., 2009), Na^+ and Ca^{2+} channel blockers (Nitsche et al., 2004), L-DOPA (Kuo et al., 2008), and the D_2 receptor agonists (Nitsche et al., 2006; Monte-Silva et al., 2009) also have an effect on increasing and/or decreasing the effects of tDCS stimulation (for more see Stagg and Nitsche, 2011). Some progress in linking DNA genotypes with cognitive performance is underway. Different genotypes reflect differences in the biology, such as neurotransmitter level or ion channel subtypes, that may affect the influence of tDCS. The catechol-*O*-methyltransferase (*COMT*) gene codes for an enzyme that metabolizes catecholamines and it is particularly important for metabolizing prefrontal dopamine. A single point mutation in the *COMT* gene (val158met) is associated with differences in cognitive abilities (de Frias et al., 2004; Bruder et al., 2005; Bertolino et al., 2006; Aguilera et al., 2008; Stokes et al., 2011; Buckert et al., 2012). There is also some evidence that *COMT* genotype has a significant effect on the volume of gray matter and parietal lobe activity (Dumontheil et al., 2011). Consequently, *COMT* genotype may play a role in determining how participants will respond to tDCS, or whether they have a low or high WM capacity. This complex story will require collaboration between neuroscientists focusing on all of these levels to enable accurate prediction of the effect of tDCS.

There are also discrepancies between studies in the tDCS literature that deserve mention. The relationship between stimulation condition and its effects are not fully understood. The assumption with tDCS in studies of cognition is that there is an excitatory effect of anodal current and an inhibitory effect of cathodal current. As shown in a recent meta-analysis this is commonly observed in studies of motor cortex stimulation, but this pattern is only rarely seen in studies of cognition (Jacobson et al., 2012). One explanation for this are that cognitive abilities are more active than motor functions during stimulation as participants are generally not moving but still have active WM. Motor behavior is not voluntarily activated during stimulation whereas WM is constantly being updated. Measures of cognitive task performance may also be more susceptible to external noise than measures of motor task performance. This may be because motor tasks are generally measured with motor evoked potentials whereas cognitive performance is measured by a variety of ways such as reaction time, accuracy, and neuroimaging (e.g., fMRI, ERP, and MEG; further reviewed in Jacobson et al., 2012). Some examples of studies of cognitive functions that do not follow the anodal-excitatory, cathodal-inhibitory pattern are picture naming (Monti et al., 2008), risk-taking (Boggio et al., 2010), and reaction time on a visual Sternberg task (Marshall et al., 2005). Also, cathodal tDCS may not be decreasing neural excitability, but it may be reducing competition between neurons (Antal et al., 2004b). Another explanation is that cathodal tDCS to the right PPC acts as a noise filter and helps to suppress distractors and boost performance (Weiss and Lavidor, 2012). This predicts a greater benefit of tDCS at greater set sizes, consistent with our finding that there was a greater benefit at set size 8 than 4 or 6.

Limitations and open questions

One limitation of the present analysis is that we conducted a median split based on the combined digit span scores. Median splits eliminate the continuous nature of the digit span variable. Future individual differences investigations will be needed to more precisely assess the relationship between WM capacity and parietal lobe involvement in WM tasks. These findings show that at the coarser group level there are differences. We speculate that the nature of these differences may be reflecting different strategies in accomplishing WM tasks. Another criticism is that we assessed WM capacity based on digit span scores. It has been suggested that the digit span measure does not correlate as well as complex WM span tasks with fluid intelligence (Chein et al., 2011). Complex WM span tasks require attention to shift away from the to-be-remembered items to perform a second distracter task. This is a more realistic representation of the way WM operates in everyday life. To address this concern we have begun to collect Operation span measures (Turner and Engle, 1989; Unsworth and Engle, 2005) from our participants in addition to forward and backward digit span. Operation span task requires participants to remember a series of words interleaved with distracter arithmetic equations. We conducted this measure on 16 of the 28 participants. Analyses conducted based on these scores were consistent with groups defined by digit span. To date, people who have been

tested on both measures reveal the same pattern of data. This provides some assurance that dividing groups based on digit span is likely to produce similar results.

A second limitation of this work is that tDCS cannot claim to focally stimulate a particular aspect of the PPC. We were careful to use this overly general term even though the PPC is clearly composed of multiple functional subsections – e.g., the superior parietal lobule, supramarginal gyrus, and angular gyrus. This problem of identifying the site of tDCS stimulation is currently being addressed through the application of cortical modeling (Datta et al., 2009a, 2011; Mendonca et al., 2011). These modeling data can provide considerable insight to the unintuitive spread of current through the cortex. For our purposes, the between-subjects findings are important because the same electrode montages were applied to all participants. Consequently, even though we cannot state with precision the boundaries of stimulation, we can state that there were differential effects as a function of WM capacity. In the future the development of High Density tDCS (HD-tDCS) techniques will permit greater specificity in estimating the extent and specificity of cortical stimulation (Datta et al., 2009b; Diaz et al., 2009; Dmochowski et al., 2011). The combination of cortical modeling and HD-tDCS will supplement the researcher's armamentarium and provide an effective and safe investigational tool to probe brain structure–function relationships.

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Modulation of untruthful responses with non-invasive brain stimulation

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Deceptive abilities have long been studied in relation to personality traits. More recently, studies explored the neural substrates associated with deceptive skills suggesting a critical role of the prefrontal cortex. Here we investigated whether non-invasive brain stimulation over the dorsolateral prefrontal cortex (DLPFC) could modulate generation of untruthful responses about subject's personal life across contexts (i.e., deceiving on guilt-free questions on daily activities; generating previously memorized lies about past experience; and producing spontaneous lies about past experience), as well as across modality responses (verbal and motor responses). Results reveal that real, but not sham, transcranial direct current stimulation (tDCS) over the DLPFC can reduce response latency for untruthful over truthful answers across contexts and modality responses. Also, contexts of lies seem to incur a different hemispheric laterality. These findings add up to previous studies demonstrating that it is possible to modulate some processes involved in generation of untruthful answers by applying non-invasive brain stimulation over the DLPFC and extend these findings by showing a differential hemispheric contribution of DLPFCs according to contexts.

Keywords: deception, dorsolateral prefrontal cortex, brain stimulation, verbal communication

INTRODUCTION

Deception is generally defined as deliberately intending to mislead another person by falsification of truthful information (Vrij, 2001; DePaulo et al., 2003; Spence et al., 2004). Several types of deception exist, but they all seem to share a complex neural network with the prefrontal cortex as putative conductor (e.g., Spence et al., 2004; Gombos, 2006). Deceptive abilities appear early in ontogenesis and parallel the developmental course of intricate complex social and communication behaviors along with maturity of executive functions, especially inhibitory control. Although humans are experts at deceiving (lying seems to be a daily life event: DePaulo et al., 2003), it generally requires additional cognitive processing than being truthful (Spence et al., 2004; Gombos, 2006; Vrij et al., 2006; but see DePaulo et al., 2003). The more complex a lie is, the greater the cognitive load (Vrij and Mann, 2001). Various behavioral cues have been identified and suggested to be a signature of this increased cognitive burden. For instance, verbal (e.g., increased pauses; Mann et al., 2002; DePaulo et al., 2003; Vrij, 2005), vocal (e.g., higher pitch; DePaulo et al., 2003), and non-verbal cues (e.g., reduced bodily movements, increased gaze aversion; Vrij and Mann, 2001; Mann et al., 2002; DePaulo et al., 2003; Nunez et al., 2005) have been noted during false statements. However, reliability of these cues to discriminate deceptive from truthful responses remain very poor (Vrij, 2001; DePaulo et al., 2003; Masip et al., 2003; Vrij et al., 2006, 2007, 2008).

One indicator of deceit that has shown consistency in experimental setting is latency of response time. It takes longer to provide untruthful than truthful answers (Spence et al., 2001, 2004; Farrow et al., 2003; Walczyk et al., 2003; Johnson et al., 2004, 2007; Nunez et al., 2005). Moreover, it is difficult to alter response latency by strategic manipulation, like other cues such as gaze aversion or body gesture. Despite being informed on how to modulate their response time, subjects failed at mitigating this response time effect (Seymour et al., 2000). Even the level of stake (Vrij et al., 2008), motivation, and transgression (DePaulo et al., 2003) do not appear to influence this lengthened response time (but see Verschuere et al., 2009).

The objective of this work was to investigate whether this lengthening in response latency associated with untruthful answers can be modulated using transcranial direct current

stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) across contexts and modality responses. The overreaching neurobiological conceptualization here is the idea that deceptive behaviors regardless of contexts can be learned and trained involving the DLPFC. A better understanding of the role of the DLPFC in deception is important because it may also shed light on impaired neurobehavioral substrates in populations who are disabled with compulsive deception (e.g., antisocial personality disorder).

We conducted a series of experiments with healthy volunteers to assess the effects of tDCS over the DLPFC in three different contexts: (1) generating untruthful answers about daily personal information that does not elicit significant guilt (Task 1), (2) generating a coherent lie that was previously memorized, and (3) producing spontaneously a coherent lie (Task 2). Control experiments included a task on the ability to generate spontaneous verbal responses (Task 3) and the Stroop interference (Task 4). Personality profiles were characterized with the Psychopathic Personality Inventory (PPI).

MATERIALS AND METHODS

Thirty-six subjects (11 men; three left-handed; mean age of 21.6 ± 3.8 years) took part in the study, which comprised three experimental tasks and two control tasks. Although studies have reported bilateral prefrontal activations, including in DLPFCs, associated with deceptive answers with a right dominance and have been correlated with response latency (e.g., Gamer et al., 2007), the hemispheric contribution is not clear yet (e.g., Spence et al., 2004). We therefore included three types of electrode arrangements. One arrangement was with the anodal electrode placed over the right DLPFC coupled with the cathodal electrode over the contralateral DLPFC (referred here as 'right anodal/left cathodal'), which is known to enhance excitability in the right DLPFC and decrease it in the left DLPFC. A second stimulation condition was with the anodal electrode placed over the left DLPFC coupled with the cathodal electrode over the contralateral DLPFC (referred as 'left anodal/right cathodal') and is known to activate the left and suppress the right DLPFC excitability. The third condition was a sham stimulation control with both electrodes placed over the DLPFC (half of the subjects with the sham left anodal/right cathodal arrangement, the other half with the sham right anodal/left cathodal arrangement). Subjects were pseudo-randomly assigned to receive either right anodal/left cathodal ($N = 12$; five men; one left-handed; mean age of 22.2 ± 3.3 years), left anodal/right cathodal ($N = 12$; 2 men; one left-handed; mean age of 20.3 ± 1.9 years), sham stimulation ($N = 12$; four men; one left-handed; mean age of 22.4 ± 5.4 years). All participants were college students. They were not taking medications, had no history of neurological or psychiatric disorders and had normal physical and neurological exams. They were screened for contraindications for non-invasive brain stimulation. All were naive to brain stimulation and were not informed about the main experimental variables tested (i.e., response latencies). They gave informed written consent prior to entering the study, which was approved by the local ethics committee. The study was performed at Mackenzie University (Sao Paulo, Brazil).

Each participant performed a total of four tasks (see **Figure 1**). The order of tasks was counterbalanced across subjects. Pre-testing was done before stimulation and then all tasks were tested one after the other after stimulation. The four tasks were completed within 30 min after the end of stimulation. The four tasks, as well as the PPI, were administrated by investigators blinded to stimulation condition and experimental variables tested.

EXPERIMENTAL TASK 1: GENERATING UNTRUTHFUL RESPONSES ABOUT PERSONAL DAILY ACTIVITIES

The goal of Task 1 was to test whether tDCS over the DLPFC could modulate untruthful answers in the context of personal daily activities. This task was based on Spence et al. (2001). Before brain stimulation (the same day), participants filled out a form that included 33 questions about their personal daily activities (Instructions: "In the course of today, have you done any of the following?"; see **Figure 1**). This form provided us with *truthful* answers about each participant's daily activities. After receiving brain stimulation, participants were asked to answer (*yes*/*no*) on their daily activities according to the cue provided on a computer screen (*truth*/*lie*). The questions were the same as those asked before stimulation. Each question was asked twice, half presented with the cue *truth*, the other half with the cue *lie*. Questions were auditorily presented and subjects had to give a motor response using the computer keyboard. Half of the subjects had to press the key "v" for *yes* and the key "b" for *no*, the other half had to press the opposite key setting: "b" for *yes* and "v" for *no*. The order of the questions and the cues was pseudo-randomized. Level of guilt to lie about these activities was judged from an independent group of healthy volunteers ($N = 5$; two men; mean age 28.3 ± 2.5 years) on visual analog scales (with "0" defined as *not at all* and "100" as *very much*). Average rating of level of guilt of all questions was 17.6% (SD = 23.3%).

EXPERIMENT TASK 2: DECEIVING ABOUT PERSONAL PAST EXPERIENCE

The aim of Task 2 was to test whether tDCS over the DLPFC could change untruthful responses about personal past experience with either memorized lies or spontaneous lies. This experiment was based on work from Ganis et al. (2003). Immediately before stimulation, subjects were asked to fill out a questionnaire (see **Figure 1**). The questions were: (1) what is the best movie you have seen, where, when and with whom did you see it, and (2) what is the best show you have seen, where, when, and with whom did you see it. They were then asked to make up plausible lies to these same questions and to memorize them because they would be asked after stimulation to retrieve these memorized lies. After stimulation, they had to answer the same questions (e.g., what is the best show you have seen?) three times according to the cue provided (*truth*, *memorized lie*, and *spontaneous lie*). The questions were auditorily presented for maximizing ecological validity and subjects had to provide a verbal answer.

CONTROL TASK 3: GENERATION OF SPONTANEOUS VERBAL RESPONSES

In this control task, we tested for possible effects of tDCS over DLPFC on the ability to spontaneously generate verbal responses as it has been shown that TMS over DLPFC can reduce response

time on verbal fluency tasks (Iyer et al., 2005). Participants had to provide a viable response to nine open-ended questions. The instructions were "Here are different scenarios. You have to come up with a plausible answer for each scenario. Try to be as convincing as possible. Your answers will be recorded and there will be individuals, who do not know that all of your answers are all made up answers, who will try to identify which of your answers are truthful. Here is an example: Someone is asking you to use your computer and you do not want him to use it because…". The scenarios were audio-recorded and subjects had to provide a verbal answer thus maximizing ecological validity as in Task 2. The order of the scenarios was pseudo-randomized.

CONTROL TASK 4: STROOP INTERFERENCE

We tested for possible effects of brain stimulation on inhibitory control functions using the Stroop task. Stimulation over the DLPFC likely modulates activity also in neighboring regions such as the orbitofrontal area, which is involved in inhibitory control functions (Elliot and Deakin, 2005). Modulation of inhibitory functions could impact deceptive skills that would not be specific to the ability of being deceptive. Participants were therefore asked to perform the Stroop task, a standardized paradigm to measure non-specific inhibitory control related to prefrontal cortex, before and after stimulation. We measured the Stroop interference, which is characterized by slower response in naming incongruent words (i.e., the word *red* printed in green ink) as compared to color congruent words (Stroop, 1935).

PSYCHOPATHIC PERSONALITY INVENTORY

Personality profile of participants was assessed because personality traits may contribute to the ability of deceiving. To test for possible differences in personality features between groups, participants filled out the PPI (Lillienfeld and Andrews, 1996) before the stimulation session. The PPI comprises eight subscales: Machiavellian egocentricity, social potency, fearlessness, coldheartedness, impulsive non-conformity, blame externalization, carefree non-planfulness, and stress immunity.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Direct current was induced by two saline-soaked surface sponge electrodes (35 cm^2) and delivered in a double-blinded fashion by a battery-driven, constant current stimulator. The device used, developed by our group, is particularly reliable for double-blind studies: a switch can be activated to interrupt the electrical current while maintaining the *ON* display and showing the stimulation parameters throughout the procedure to the experimenter and participant. For right anodal/left cathodal stimulation, the anode electrode was placed over right F4 (international EEG 10/20 system) and the cathode electrode over left F3. For left anodal/right cathodal stimulation, the polarity was reversed: the anode electrode was placed over F3 (EEG 10/20 system) and the cathode electrode over F4. For active stimulation, participants received a constant current of 2 mA intensity. Stimulation was delivered for 20 min and participants performed the tasks immediately after the end of the stimulation session. For sham stimulation, the

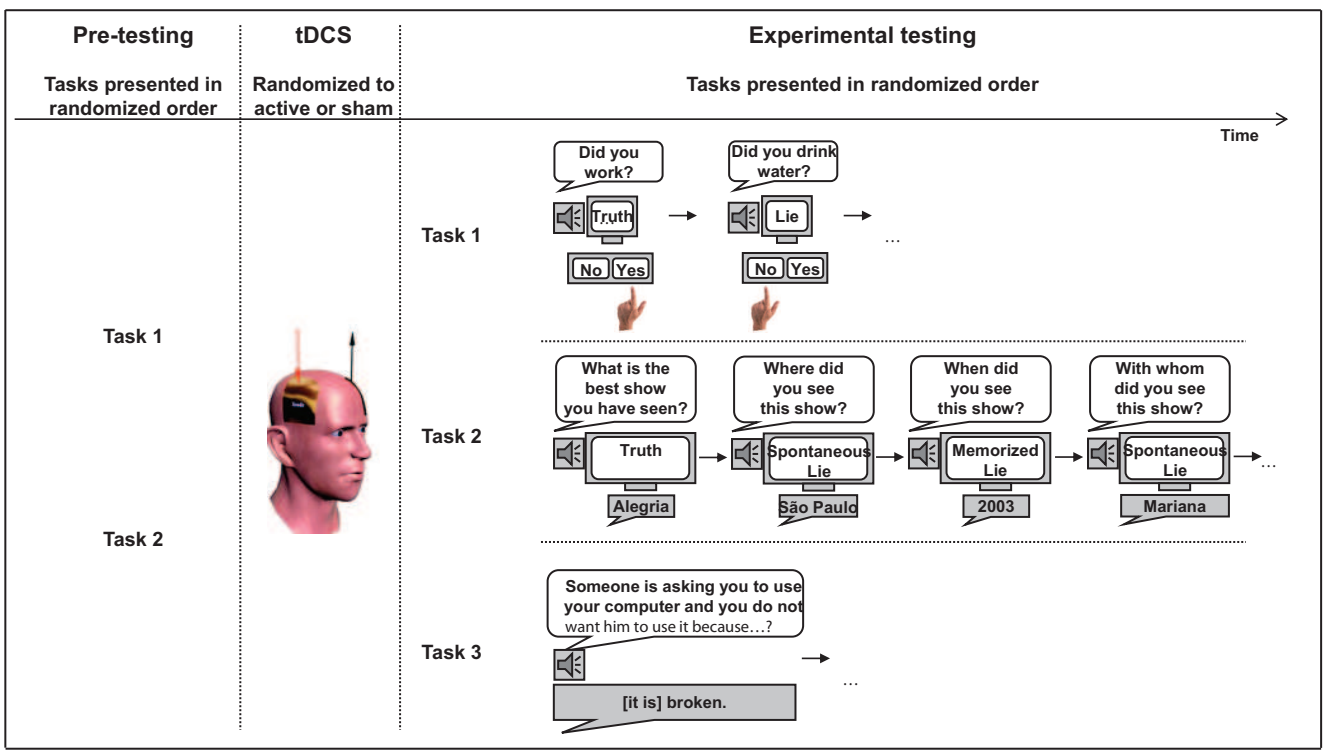

FIGURE 1 | Design of the study. Participants first performed Tasks 1 and 2 (prior stimulation), they then received active or sham tDCS, and they finally performed Tasks 1 and 2 again, as well as the Task 3.

electrodes were placed at the same position as for active stimulation (F3 and F4), but the stimulator was turned on only for the first 30 s so participants felt the initial itching sensation associated with the stimulation, but received no active current for the rest of the stimulation period. This method of sham stimulation has been shown to be reliable (Gandiga et al., 2006).

DATA ANALYSIS

Tasks 1, 2, and 3 were administrated using PsyScope software X B41 running on a PowerBook G4 (Apple Inc., Cuppertino, CA, USA).

In Task 1 (Generating untruthful responses about personal daily activities), the outcome measure was the difference in motor response latency in milliseconds between the lie and truth conditions. Only response latencies of *correct* answers at both lie and truth conditions were analyzed based on participants' information on their daily activities collected before brain stimulation. Response latencies were then averaged for each subject and across stimulation conditions. Due to technical problems during Task 1, data from three subjects were not recorded (one in the right anodal/left cathodal, one in the left anodal/right cathodal, and one in the sham group).

In Task 2 (Generating untruthful responses about personal past experience) and in Task 3 (Generation of spontaneous verbal responses), the outcome measure was the verbal response latency, i.e., time elapse between the end of the verbal question and the onset of subjects' correct (memorized lies) or coherent, plausible answer (spontaneous lies and spontaneous verbal responses). Only one response was excluded because it was not plausible: "Bob Marley" (Task 2). Vocal answers were recorded using Voice Editing Premium Edition recorder (Panasonic Corporation). Response latency was calculated as the time between the end of the instruction and the onset of the first word produced by the subject. Filler words such as "my friend. . ." were discarded. Response latency was measured in milliseconds using PRAAT (http://www.praat.org) and then averaged across conditions: truth, memorized lies, spontaneous lies, and spontaneous verbal responses.

For all experiments, response latencies were measured by two individuals blinded to stimulation condition. Outliers, defined as 2 SD above or below individual mean of onset of response latency for each condition and participant, were excluded. Analyses were performed using SAS (SAS Institute Inc, NC, USA). Results with a p-value of ≤ 0.05 were considered significant for all statistical analyses.

RESULTS

None of the volunteers reported adverse effects during or after brain stimulation. Most participants perceived a slight itching sensation under the electrodes during the first seconds of stimulation. When explicitly asked at the end of the study whether they believe having received active or sham stimulation, all participants believed to have undergone active stimulation, suggesting successful blinding of the sham stimulation condition.

EXPERIMENTAL TASK 1: GENERATING UNTRUTHFUL RESPONSES ABOUT PERSONAL DAILY ACTIVITIES

In Task 1, there was a main effect of stimulation group on response latency [untruthful versus truthful answers; ANOVA; $F_{(2,30)} = 3.68$; $p = 0.037$]. This is illustrated in **Figure 2**. Bonferroni *post hoc* analysis revealed a difference between the right anodal/left cathodal and sham groups ($p = 0.036$): participants who received right anodal/left cathodal stimulation showed smaller difference in response latency between untruthful and truthful answers as compared to participants who received sham stimulation. There was no significant latency difference between the left anodal/right cathodal and sham groups ($p = 0.27$) and no difference between the two active groups ($p > 0.1$). Also, there was no significant latency difference between women and men ($p > 0.1$). For accuracy (i.e., the number of correct pairs of answers), results revealed no significant group difference across groups (78% of correct pairs for the right anodal/left cathodal group; 85% correct pairs for the left anodal/right cathodal group; and 84% correct pairs for the sham group; $p > 0.1$).

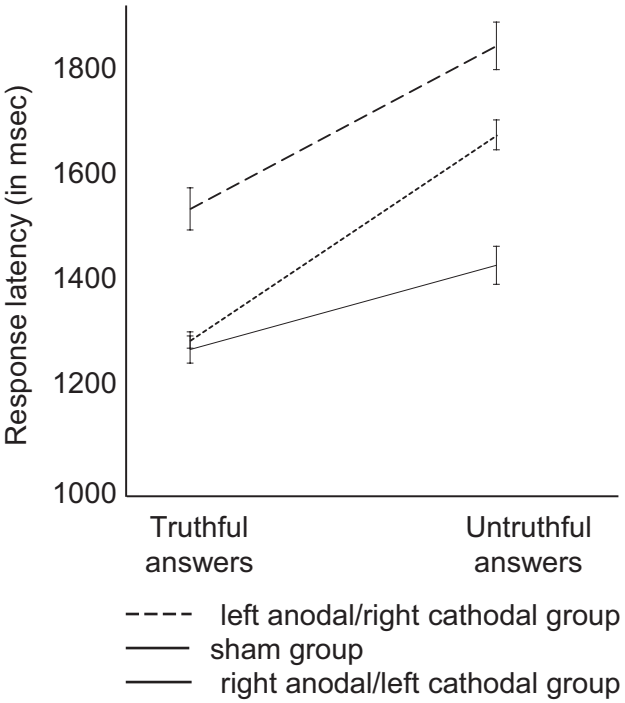

FIGURE 2 | Averaged response latency of truthful and untruthful answers for each group of participants in Task 1. Participants who received right anodal/left cathodal DLPFC stimulation showed smaller difference in response latency between truthful and untruthful answers (difference of 185 ms) than the left anodal/right cathodal (difference of 358 ms) and sham groups (difference of 449 ms). Error bars represent SEM.

EXPERIMENTAL TASK 2: DECEIVING ABOUT PERSONAL PAST EXPERIENCE

Generating untruthful responses about personal past experience with memorized lies

Results of deception with *memorized lies* revealed an effect of stimulation group on response latency [ANOVA; $F_{(2,35)} = 4.593$; $p = 0.017$]. Bonferroni *post hoc* analysis revealed a significant difference between the sham and the left anodal/right cathodal groups ($p = 0.035$), as well as between the sham and the

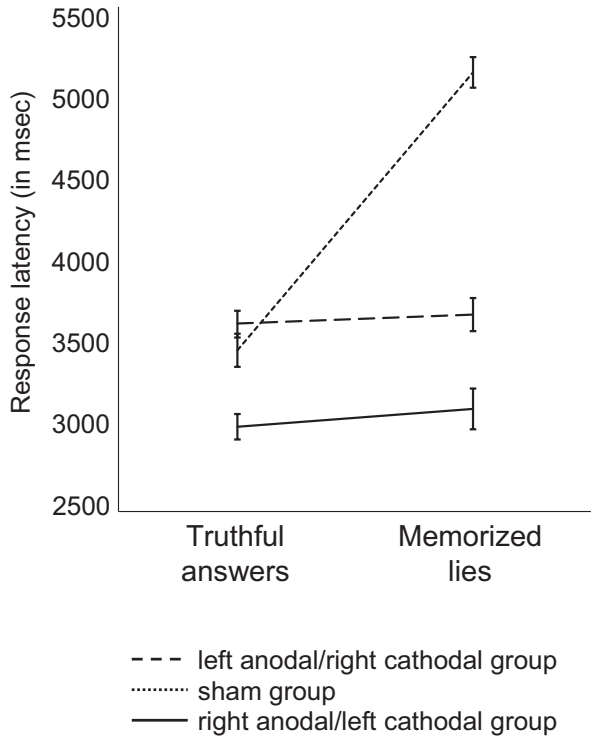

FIGURE 3 | Averaged response latency of truthful answers and memorized lies for each group of participants in Task 2. Participants who received active DLPFC stimulation were faster at retrieving memorized lies as illustrated by smaller difference in response latency between truthful and memorized lies (right anodal/left cathodal DLPFC stimulation: difference of 10 ms; left anodal/right cathodal DLPFC stimulation: difference of 6 ms) than the sham groups (difference of 166 ms). Error bars represent SEM.

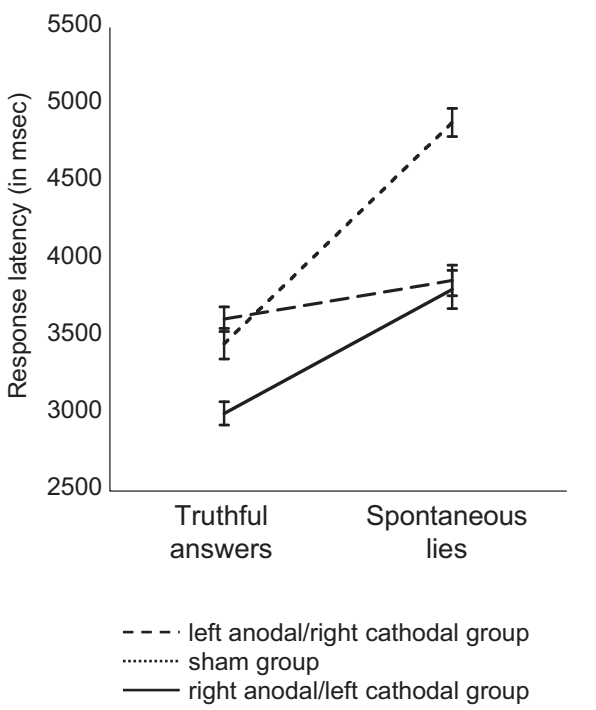

FIGURE 4 | Averaged response latency of truthful answers and memorized lies for each group of participants in Task 2. Participants who received left anodal/rightt cathodal DLPFC stimulation were faster at generating spontaneous lies, showing smaller difference between truthful answers and spontaneous lies (difference of 25 ms) than participants who received sham stimulation (difference of 143 ms) and right anodal/left cathodal DLPFC stimulation (difference of 80 ms). Error bars represent SEM.

right anodal/left cathodal groups ($p = 0.044$). As illustrated in **Figure 3**, response latency difference between memorized untruthful and truthful responses was significantly smaller in subjects who received active stimulation as compared to those who received sham stimulation. There was no difference in response latency between women and men ($p > 0.1$). For accuracy, there was no effect of stimulation group ($p = 0.095$) and no effect of condition ($p > 0.1$). Participants with left anodal/right cathodal, right anodal/left cathodal, and sham stimulation provided correct truthful answers at 92% (SEM = 0.7), 88% (SEM = 1.1), and 82% (SEM = 1.2), respectively, and correct memorized lies at 94% (SEM = 0.8), 91% (SEM = 1.0), and 91% (SEM = 1.1), respectively.

Generating untruthful responses about personal past experience with spontaneous lies

Results of generating untruthful responses *with spontaneous lies* revealed an effect of stimulation group in response latency [ANOVA; $F_{(2,35)} = 3.530$; $p = 0.041$]. Bonferroni *post hoc* analysis revealed a significant difference in response latency between the sham group and the left anodal/right cathodal stimulation group ($p = 0.036$), but no significant difference between the right anodal/left cathodal and sham groups ($p > 0.1$). As shown in **Figure 4**, response latency difference between spontaneous untruthful and truthful responses was smaller in subjects who received active stimulation as compared to that who received sham stimulation. There was no difference in response latency between women and men ($p > 0.1$). For accuracy (i.e., the number of coherent untruthful answers), results revealed no effect of stimulation group ($p = 0.094$) and no effect of condition ($p > = 0.1$). Participants with left anodal/right cathodal, right anodal/left cathodal, and sham stimulation provided correct truthful answers at 92% (SEM = 0.7), 88% (SEM = 1.1), and 82% (SEM = 1.2), respectively, and coherent spontaneous lies at 75% (SEM = 1.3), 80% (SEM = 2.0), and 80% (SEM = 1.9), respectively.

CONTROL TASK 3: GENERATION OF SPONTANEOUS VERBAL RESPONSES

For the control verbal task, there was a no group effect on response latency [ANOVA; $F_{(2,35)} = 2.850$; $p = 0.072$]. For the number of words, groups did not significantly differed [ANOVA; $F_{(2,35)} = 0.40$; $p > 0.1$]. Volunteers receiving right anodal/left cathodal stimulation produced an average of 7.2 words (SEM = 0.5), those with left anodal/right cathodal stimulation produced an average of 9.5 words (SEM = 0.6), and those with sham stimulation an average of 6.5 words (SEM = 0.3).

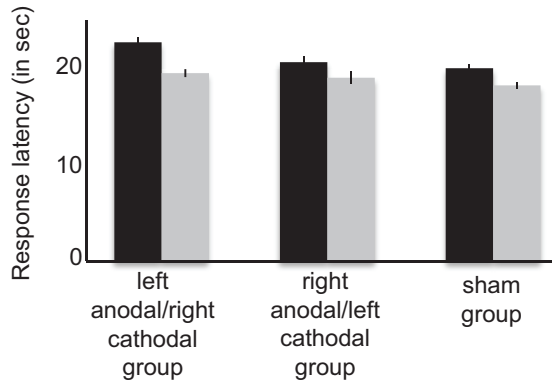

FIGURE 5 | Averaged response latency for each group of participants at the Stroop interference task. Participants were faster when they performed the task the second time as compared as the first time, regardless of their stimulation condition. Error bars represents SEM.

CONTROL TASK 4: STROOP INTERFERENCE

For the Stroop task, response latencies were submitted to a repeated measures ANOVA with time of assessment (pre-tDCS, post-tDCS) as within-subjects factor and stimulation groups (right anodal/left cathodal stimulation group, left anodal/right cathodal stimulation group, and sham group) as between subject factor. There was an effect of time of assessment [$F_{(1,11)} = 16.973$; $p < 0.002$], no effect of stimulation group [$F_{(2,22)} = 0.139$; $p > 0.1$], and no interaction between time and group [$F_{(2,22)} = 0.484$; $p > 0.1$] was observed. The effect of time of assessment reflects faster color naming on the second assessment in all three groups of subjects, likely due to repeated testing (**Figure 5**).

PSYCHOPATHIC PERSONALITY INVENTORY

For the personality profile assessed in participants prior stimulation, there was no group difference for the total PPI score [ANOVA; $F_{(2,61)} = 0.298$; $p > 0.1$] and all the subscales ($p > 0.1$), except for the coldheartedness ($p = 0.017$) and stress immunity subscales ($p = 0.001$). Bonferroni *post hoc* analysis revealed for the coldheartedness subscale a difference between the right anodal/left cathodal and left anodal/right cathodal groups ($p = 0.014$), but no difference between the right anodal/left cathodal and sham groups ($p > 0.1$), or between the left anodal/right cathodal and sham groups ($p > 0.1$). For the stress immunity subscale, there was a difference between the right anodal/left cathodal and left anodal/right cathodal groups ($p = 0.001$) and between the left anodal/right cathodal and sham groups ($p = 0.029$), but no difference between right anodal/left cathodal and sham groups ($p > 0.1$). Scores are presented in **Table 1**.

DISCUSSION

Results from this work revealed that non-invasive brain stimulation with tDCS over the DLPFC can modulate production of untruthful answers about subject's personal life. We observed a reduced response latency associated with untruthful answers, one of the most reliable cues for identifying lies. Our results extend findings from prior brain stimulation studies. In Priori et al. (2008), tDCS over the right DLPFC coupled with anodal/cathodal reduced response latency when subjects had to report through a motor response that they had not seen a picture when they had been previously presented with the picture. In Karim et al. (2009), response latency was shorter in subjects who receive tDCS over the anterior prefrontal cortex when they had to lie at the Guilty Knowledge Test. In Mameli et al. (2010), healthy subjects receiving active anodal tDCS over the both DLPFC cortices were faster at providing lies on general knowledge as compared to that before stimulation. This effect was not observed on lies involving personal information. From an evolutionary point of view, our results and the prior findings support the idea that deception is a relatively new cognitive and neural development (e.g., Premack, 2007), that is a learned behavior that can be influenced via the DLPFC, a highly plastic brain region.

A further novel finding from our work is that the hemispheric contribution was different according to contexts. Right anodal/left cathodal DLPFC stimulation resulted in improvement for generating untruthful answers of relatively guilt-free personal questions on daily activities through motor responses (Task 1) and generating memorized untruthful answers about subjects' past through verbal responses (Task 2 with memorized lies). The opposite electrode arrangement (left anodal/right cathodal) also improves deceptive skills but only for generating spontaneous and memorized untruthful answers about subjects' past experience (Task 2). Brain imaging studies contrasting truthful with deceptive answers, found enhanced activity in *bilateral* Brodman Area (BA) 47 in the task we used in Task 1 (Spence et al., 2001), in *bilateral* BA 10 in the task we used in Task 2 with memorized lies, and in *bilateral* BA 10 and right BA 9 in the task we used in Experiment 2B (Ganis et al., 2003). However, our results reveal a laterality to the contributions. In Karton and Bachmann (2011), subjects tended to lie more often were they received repetitive transcranial magnetic stimulation over the left, as compared to the right DLPFC in a task in which subjects were free to lie or not. Neither the present, nor previous brain stimulation studies can conclusively establish whether the impact on deception is solely due to the modulation of activity in one DLPFC, or the result of changing the balance of activity across both DLPFCs as brain activity was not measured. Findings are most cautiously interpreted as a result from modulation of a functionally connected network, with DLPFC as a primary modulated areas, likely including the orbitofrontal area, which has also been involved in deception (Spence et al., 2001, 2004; Ganis et al., 2003). We believe also that it is too soon to speculate on the specific role of each DLPFC in deceptive abilities, but our results suggest a differential contribution according to contexts. Future work should use single electrode arrangement and/or combine non-invasive brain stimulation with neuroimaging to identify the key network involved in deceptive abilities.

There are various cognitive processes required to generate untruthful answers in the present experiments that might have been modulated by tDCS. The cognitive demand required for being deceptive in the present experiments follows to some extent Walczyk et al.'s (2003) model. According to this model, for lies to be produced, cognitive processes control actions in the following way: (1) working memory first activates knowledge of the truth; (2) then decision-making processes are elicited to determine

Table 1 | Scores for each participant at the Psychopathic Personality Inventory.

tDCS	ID	Total score	Machiavellian egocentricity	Social potency	Fearlessness	Coldheartedness	Impulsivity non-conformity	Alienation	Carefree non-planfulness	Stress immunity
RA/LC	1	422	65	94	63	39	41	42	41	32
LA/RC	2	302	58	40	32	36	29	38	39	24
SR	3	317	46	52	35	35	33	37	43	30
RA/LC	4	408	75	62	43	48	47	50	48	28
LA/RC	5	331	59	52	40	44	35	27	46	22
SL	6	357	66	62	46	34	34	42	45	22
RA/LC	7	342	51	50	48	45	34	38	45	25
LA/RC	8	401	70	75	47	39	45	47	49	21
SR	9	323	63	51	34	35	35	30	45	22
RA/LC	10	322	56	48	39	49	28	23	41	35
LA/RC	11	351	60	55	49	34	40	36	50	22
SL	12	375	78	56	45	50	41	39	33	27
RA/LC	13	398	63	67	57	49	41	38	44	31
LA/RC	14	385	68	72	55	25	46	49	41	24
SR	15	344	54	72	47	36	38	35	29	26
RA/LC	16	334	50	53	43	39	39	35	39	30
LA/RC	17	311	52	53	46	37	38	24	35	20
SL	18	349	73	47	45	35	29	42	39	30
RA/LC	19	340	75	58	30	39	32	37	39	25
LA/RC	20	380	67	76	46	28	39	48	48	19
SR	21	323	54	60	34	35	43	25	43	25
RA/LC	22	291	53	39	38	26	35	39	42	16
LA/RC	23	383	70	64	45	44	41	45	37	30
SL	24	343	66	53	45	39	40	29	38	23
RA/LC	25	312	55	57	32	33	29	41	34	26
LA/RC	26	382	72	56	40	35	50	54	48	20
SR	27	360	67	69	48	35	32	39	34	29
RA/LC	28	310	66	37	31	38	31	43	31	27
LA/RC	29	309	58	47	38	35	36	39	29	22
SL	30	333	48	50	53	35	40	35	38	29
RA/LC	31	377	61	53	64	41	43	34	46	30
LA/RC	32	351	65	65	40	37	40	40	33	28
SR	33	365	62	57	52	47	45	29	38	30
RA/LC	34	335	58	63	42	39	32	34	36	24
LA/RC	35	359	63	50	54	36	46	43	37	23
SL	36	367	57	60	56	37	45	41	38	27

whether or not to lie; (3) then inhibition is required to conceal truthful information; and (4) finally, attention processes mediate knowledge about the context in order to construct a plausible lie. Stages one through three are relevant to cognitive processes involved in Tasks 1 and 2, and stages one through four to that in Task 2 with spontaneous lies. In order to successfully lie here, cognitive processes required included:

(1) Activation of some working memory components (e.g., Task 1: *Did I drink water today?*; Task 2 (with memorized and spontaneous lies): *What was the best show I have seen?*);
(2) Following of the instruction whether or not to generate untruthful answers (task switching);
(3) Suppression of the pre-potent answer to conceal the truth when they had to untruthful answers (e.g., Experiment 1: *Yes I drank water today*; Task 2 with memorized and spontaneous untruthful answers: *The best movie I have seen is Alegria*), and finally;
(4) Generation of the response:
  4(a) Reversal of the answer in Task 1 (e.g., *No*);
  4(b) Retrieval of the memorized lie in Task 2 with memorized untruthful answers (e.g., *Quidam*);
  4(c) Construction of a novel lie in Task 2 with spontaneous untruthful answers (e.g., *Saltimbanco*).

We discuss some potential cognitive functions that might have been impacted in a different way across DLPFC stimulation conditions according to the observed improved production of untruthful responses skills. First, one could argue that DLPFC modulation might have differentially impacted working memory

load across stimulation groups. We believe this is unlikely the case. Memory has to be activated for both truthful and untruthful answers between groups. Therefore, if neuromodulation had impacted memory, there would have been a difference in latency of truthful answers, which was not observed in any of our experiments. In addition, if neuromodulation had significantly affected memory access, there would likely be a difference in the number of incorrect answers between groups. This again, was not observed.

Second, one could argue that DLPFC modulation reduced the demands of cue-elicited behavior as subjects were instructed for each trial to be untruthful or truthful as task switching can elicit activation in the prefrontal cortex (e.g., Dove et al., 2000). However, this demand was required in both deceptive and truthful conditions and subjects were not faster at providing truthful answers.

Third, an important cognitive process required for providing untruthful answers in our three experiments was to refrain from emitting relatively pre-potent responses. However inhibition was not facilitated with active tDCS over the DLPFC at the Stroop interference paradigm. If neuromodulation had changed inhibition, this facilitation would have been selective for deceptive behaviors. This would suggest that inhibitory systems are fundamentally different between inhibiting a truthful answer (even for benign white little lies as those in Task 1) and suppressing naming color incongruent words at the Stroop task.

Fourth, volunteers in Task 1 had to provide the deceptive answer by reversing the pre-potent response. Although the answer was a simple *yes* or *no* motor response, we cannot rule out that this reversal process might have been improved by right anodal/left cathodal stimulation. However, in Task 2 with memorized untruthful answers there was no such reversal of the pre-potent response and subjects were still with this same electrode arrangement (right anodal/left cathodal stimulation).

Fifth, deceptive abilities are entangled with other cognitive processes such as producing coherent and novel verbal responses, a process that was required to successfully generate untruthful answers in Task 2 with spontaneous lies. One could argue that left anodal/right cathodal stimulation might have speed up the process of generating novel information. However this was not observed in subjects who received this stimulation condition in the control experiment (*Generation of spontaneous verbal responses*). In line with this, emotional state can also be involved during deception. We cannot rule out the impact of the observed group difference of coldheartedness and stress level on untruthful answers. However, in the case of coldheartedness, the difference was between the two active groups. Thus, the improved deceptive responses between the right anodal/left cathodal stimulation and sham groups observed in Tasks 1 and 2 was unlikely due to the coldhertedness scores. For the stress immunity subscale, the difference was observed between the two active groups as well as between the left anodal/right cathodal and the sham groups. We cannot rule out that this latter difference could have played a role in the improved deceptive abilities observed in Task 2 with spontaneous untruthful answers. No group difference was however found for the total PPI score or the other subscales: Machiavellian egocentricity, social potency, fearlessness, coldheartedness, impulsive non-conformity, blame externalization, and carefree non-planfulness.

It is possible that DLPFC modulation might have reduced the overall cognitive effort usually associated with deceptive behaviors (Vrij and Mann, 2001). This effect would have been selective for generating untruthful answers as no improved performance was observed in the truthful condition, in the Stroop interference paradigm, or in the control verbal response experiment. Future experiments are warranted to measure changes in cognitive effort with brain stimulation to test whether or not it is specific to deceptive abilities. Other processes should be tested in future studies such as the act of deliberation over deception, weighting of risk and benefits, the mind of the other(s) to be lied to, and the content of the lie. Also, we studied generation of untruthful responses using cue-elicited tasks. Future studies should test shared and differential cognitive processes involved between external (as in these tasks) and internal cued lies (as done in Karim et al., 2009; Karton and Bachmann, 2011).

Of particular note, a lengthened response latency has been suggested as one the most reliable indicators of deceit to classify liars from truth-tellers (Vrij et al., 2008; see also Spence et al., 2001, 2004; DePaulo et al., 2003; Farrow et al., 2003; Nunez et al., 2005) and difficult to explicitly manipulate (Seymour et al., 2000). Here, although the length difference between being untruthful and truthful was significantly diminished after volunteers received active stimulation as compared to those who received sham stimulation, making them *better (faster)* liars, they still remained slightly slower when providing untruthful as compared to truthful answers.

We want to stress justifiable ethical and legal concerns raised by Canli et al. (2007) and Luber et al. (2009) in future work. We believe the risk-benefit ratio of understanding the neurobiological and cognitive foundation of deception and how it can be modulated is justified because it might by possible to develop protocols leading to clinical benefits in various clinical populations in which processing deception is a major disability, such as in patients with antisocial personality disorder, Parkinson's disease, or with frontal lesions. However, studies have to be conducted under proper oversight and investigators have to be aware of the potential implications of their work.

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EEG driven tDCS versus bifrontal tDCS for tinnitus

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Tinnitus is the perception of a sound in the absence of any objective physical sound source. Transcranial Direct Current Stimulation (tDCS) induces shifts in membrane resting potentials depending on the polarity of the stimulation: under the anode gamma band activity increases, whereas under the cathode the opposite occurs. Both single and multiple sessions of tDCS over the dorsolateral prefrontal cortex (DLPFC; anode over right DLPFC) yield a transient improvement in tinnitus intensity and tinnitus distress. The question arises whether optimization of the tDCS protocol can be obtained by using EEG driven decisions on where to place anode and cathode. Using gamma band functional connectivity could be superior to gamma band activity as functional connectivity determines the tinnitus network in many aspects of chronic tinnitus. Six-hundred-seventy-five patients were included in the study: 265 patients received tDCS with cathodal electrode placed over the left DLPFC and the anode placed overlying the right DLPFC, 380 patients received tDCS based on EEG connectivity, and 65 received no tDCS (i.e., waiting list control group). Repeated measures ANOVA revealed a significant main effect for pre versus post measurement. Bifrontal tDCS in comparison to EEG driven tDCS had a larger reduction for both tinnitus distress and tinnitus intensity. Whereas the results of the bifrontal tDCS seem to confirm previous studies, the use of gamma band functional connectivity seems not to bring any advantage to tDCS for tinnitus suppression. Using other potential biomarkers, such as gamma band activity, or theta functional connectivity could theoretically be of use. Further studies will have to elucidate whether brain state based tDCS has any advantages over "blind" bifrontal stimulation.

Keywords: tinnitus, EEG, tDCS, direct current, gamma

INTRODUCTION

Tinnitus is the perception of a sound or sounds (e.g., a tone, hissing, or buzzing sound, or a combination of such sounds) in the absence of any objective physical sound source (Jastreboff, 1990). In western societies about 5–15% of the population has chronic tinnitus and will seek medical attention (Axelsson and Ringdahl, 1989; Heller, 2003). Tinnitus often causes a considerable amount of distress: between 6 and 25% of the affected people report symptoms that are severely debilitating (Baguley, 2002; Eggermont and Roberts, 2004).

Based on functional imaging studies, including fMRI (Smits et al., 2007), EEG (van der Loo et al., 2009; Vanneste et al., 2010a), MEG (Muhlnickel et al., 1998; Weisz et al., 2007), and PET (Lockwood et al., 1999; Langguth et al., 2006) it is generally accepted that tinnitus is related to auditory cortex hyperactivity and maladaptive plasticity, often due to damage of the peripheral auditory system. But co-activation of non-auditory brain structures such as the insula (Smits et al., 2007; Vanneste et al., 2010a; van der Loo et al., 2011), anterior cingulate cortex (Muhlau et al., 2006; Plewnia et al., 2007; Rauschecker et al., 2010; Vanneste et al., 2010a; Leaver et al., 2011; Vanneste et al., 2011c), and dorsolateral prefrontal cortex (DLPFC; Schlee et al., 2009a; Vanneste et al., 2010a) has been described as well, and some pathophysiological mechanisms have been proposed based on these studies (Rauschecker et al., 2010; De Ridder et al., 2011a; Leaver et al., 2011). This has led to the concept that the unified tinnitus percept is the result of one large tinnitus network consisting of multiple dynamically adaptive overlapping subnetworks (De Ridder et al., 2011a), with each subnetwork representing a clinically separable aspect such as distress (Vanneste et al., 2010a; De Ridder et al., 2011b), sound characteristic (noise-like versus pure tone; Vanneste et al., 2010b), lateralization (Vanneste et al., 2011a), etc.

The DLPFC has an important function in auditory processing. Bilateral DLPFC has a facilitatory effect on auditory memory storage and contains auditory memory cells (Bodner et al., 1996). This prefrontal area also exerts early inhibitory modulation of input to primary auditory cortex in humans (Knight et al., 1989) and has been found to be associated with auditory attention (Alain et al., 1998; Lewis et al., 2000; Voisin et al., 2006) resulting in top-down modulation of auditory processing (Mitchell et al., 2005). This has been further confirmed by electrophysiological data indicating that tinnitus might occur as the result of a dysfunction in the top-down inhibitory processes (Norena et al., 1999; Faber et al., 2011).

Transcranial Direct Current Stimulation (tDCS) is an old neuromodulation tool which recently has seen a revival. In tDCS, a weak direct electrical current (1–2 mA) is applied to the scalp, through which most of the current is shunted. But about 50% of the transcranially applied direct current reaches the brain, both in animal models (Rush and Driscoll, 1968) and humans (Dymond et al., 1975). This current induces shifts in

membrane resting potentials, thereby depolarizing or hyperpolarizing neurons (Nitsche et al., 2003) depending on the polarity of the stimulation. tDCS induces an increase or decrease in cortical excitability in the brain regions to which it is applied (Nitsche and Paulus, 2000; Miranda et al., 2006). Anodal tDCS typically has an excitatory effect on the local cortical excitability by inducing a relative neuronal depolarization, while cathode has an opposite effect – it induces a hyperpolarization (Nitsche and Paulus, 2001). tDCS was first applied to the auditory cortex in an attempt to improve tinnitus (Fregni et al., 2006), and does indeed seem to be able to induce long-lasting changes in tinnitus perception (Garin et al., 2011).

Based on the influence of the DLPFC on auditory processing and its involvement in tinnitus it was demonstrated that a single session of tDCS over the DLPFC (anode over right DLPFC) yields a transient improvement in both tinnitus intensity and tinnitus distress in subjects with chronic tinnitus (Vanneste et al., 2010c), where as stimulation with anode over left DLPFC induces no changes in tinnitus (Vanneste et al., 2010c). When applying repetitive sessions this could be proposed as a treatment (Faber et al., 2011; Frank et al., 2012). The efficacy of bifrontal tDCS for transient tinnitus suppression depends on the brain state (Vanneste et al., 2011b). Applying multiple sessions of bifrontal tDCS has been proposed as potential treatment for tinnitus (Frank et al., 2012). The question arises whether optimalization of the tDCS protocol can be obtained by using EEG driven decisions on where to place anode and cathode. Based on the pathophysiology of tinnitus and the polarity dependent effect of tDCS it can be proposed to place the (inhibitory) cathode at an area of tinnitus related gamma band activity (De Ridder et al., 2007, 2011a,c; Lorenz et al., 2009; Schlee et al., 2009b; van der Loo et al., 2009), or even better gamma band functional connectivity (Vanneste et al., 2011b; Schlee et al., 2009a). Using gamma band functional connectivity could be superior to gamma band activity as functional connectivity determines the tinnitus network in many aspects of chronic tinnitus (Vanneste et al., 2010b, 2011b,d; Schlee et al., 2009b; Vanneste and De Ridder, 2011).

METHODS AND MATERIALS

PARTICIPANTS

Six-hundred-seventy-five subjects (260 males and 415 females) with chronic tinnitus (>1 year) were recruited from the Tinnitus Clinic at the University Hospital Antwerp, Belgium and participated in this retrospective study, with a mean age of 48.33 years ($Md = 50$; SD = 14.57). The mean tinnitus duration was 5.14 years ($Md = 4$; SD = 4.24). In order to obtain a homogeneous sample and exclude potential variables that would interfere with response to tDCS, we excluded subjects based on the following criteria: individuals with pulsatile tinnitus, a history of epileptic insults, severe organic co-morbidity, a pacemaker, or defibrillator, a present pregnancy, neurological disorders such as brain tumors, and individuals being treated for mental disorders. All prospective subjects underwent a complete ENT and neurological investigation to rule out possible treatable causes for their tinnitus. All patients younger than 18 years were excluded from the study. **Table 1** further shows the tinnitus characteristics for both groups. The study was in accordance with the ethical standards of the Helsinki declaration (1964) and was approved by the institutional ethics committee of the Antwerp University Hospital.

Table 1 | Tinnitus characteristics.

		Groups		
		Frontal tDCS	**EEG driven tdcs**	**Waiting list**
Mean duration		5.11	5.22	4.80
Type	Pure tone	85	134	21
	Narrow band noise	188	246	44
Laterality	Unilateral	148	214	36
	Bilateral	117	166	29

TRANSCRANIAL DIRECT CURRENT STIMULATION

Direct current was transmitted by a saline-soaked pair of surface sponges (35 cm^2) and delivered by a battery-driven, constant current stimulator with a maximum output of 10 mA (NeuroConn; http://www.neuroconn.de/). Two hundred sixty-five patients received tDCS with cathodal electrode placed over the left DLPFC and the anode placed overlying the right DLPFC, 380 patients received tDCS based on EEG connectivity. Patients who received tDCS were randomly assigned to DLPFC tDCS or tDCS based on EEG. In addition 65 received no tDCS, and were used as a waiting list control group.

For the EEG driven tDCS, EEGs (Mitsar, Saint Petersburg, Russia) were obtained 1 week before the tACS stimulation in a fully lighted room with each participant sitting upright in a comfortable chair. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 O2) in the standard 10–20 International placements referenced to linked lobes and impedances were checked to remain below 5 kΩ. Data were collected for 100 2-s epochs eyes closed, sampling rate = 1024 Hz, and band passed 0.15–200 Hz. Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz. These data were transposed into Eureka! Software (Congedo, 2002), plotted and carefully inspected for manual artifact rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifacts were removed from the stream of the EEG.

TARGET LOCALIZATION

To determine the precise location of the gamma band functional connectivity, i.e., lagged phase synchronization is used. This was operationally defined as the brain area retrieved on source localized EEG, using sLORETA software, in each individual, which has most connectivity lines in the gamma band (30–45 Hz). This measure is threshold invariant (when increasing the threshold the amount of functional connections will decrease in all areas, but the area with most connections will remain the area with most functional connections) and clinically applicable. The brain area with the highest gamma band functional connectivity was elected as the target for cathode placement. The area for placing the anode was determined by the highest theta band functional connectivity.

Connectivity can be calculated by analyzing phase synchronization or coherence. However, any measure of dependence is

highly contaminated with an instantaneous, non-physiological contribution due to volume conduction (Pascual-Marqui, 2007a). Therefore, Pascual-Marqui, (Pascual-Marqui, 2007b) introduced a new technique (i.e., Hermitian covariance matrices) that removes this confounding factor. As such, this measure of dependence can be applied to any number of brain areas jointly, i.e., distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between the multivariate time series are defined. The measures are expressed as the sum of lagged dependence and instantaneous dependence. The measures are non-negative, and take the value zero only when there is independence and are defined in the gamma (30.5–45 Hz) frequency domain. Thus only the lagged phase synchronization is used. Regions of interest were defined based on previous brain research on tinnitus (see **Table 2** for overview). Based on the functional connectivity analysis the region which forms a hub (i.e., ROI that is connected with the most ROI) is selected as the target area to be stimulated.

EVALUATION

A visual analog scale for tinnitus intensity ("How loud is your tinnitus?: 0 = no tinnitus and 10 = as loud as imaginable") and tinnitus distress ("How stressful is your tinnitus? 0 = no distress and 10 = suicidal distress") was asked before (pre) and directly after (post) tDCS stimulation. The responses were collected by the person who applied the tDCS.

STATISTICAL ANALYSES

A three-stage analysis was performed. First the overall results were calculated to verify whether there was an effect obtained by tDCS in comparison to baseline. This is followed by a second analysis evaluating whether there was a difference between frontal and EEG driven tDCS. This is then followed by a third analysis looking at the response rate and response size differences between bifrontal and EEG driven tDCS. Calculations were performed using SPSS 18.0 software package.

Overall effects

A repeated measure ANOVA was conducted with VAS distress and VAS intensity pre-tDCS and post tDCS as within-subjects variables and condition (frontal tDCS, EEG driven tDCS, and waiting list) as between-subjects variable. To verify that the within-variables were normally distributed a Kolmogorov–Smirnov test was applied. This demonstrated that the within-variables did not deviate from a normal distribution. In addition we reported the effect size by including the partial eta squared (η^2). The standards for these effect sizes are small ($\eta^2 = 0.01$), medium ($\eta^2 = 0.06$), and large ($\eta^2 = 0.14$).

A comparison between the effects obtained for frontal and EEG driven tDCS

A second repeated measures ANOVA was conducted with the obtained difference (Pre – Post tDCS) as within-subjects variable and group (Frontal tDCS versus EEG driven tDCS) as between-subjects variable to verify whether there was a significant difference in the obtained suppression on both distress and intensity. In addition we also reported the effect size by including the partial eta squared (η^2).

The effects for responders only

We applied a logistic regression with condition (including frontal tDCS and EEG driven tDCS) as independent variable and responding (No = 0 or Yes = 1) as dependent variable. Responders are defined as patients who obtain minimally 10% suppression, while non-responders are defined as those patients obtain less than 10% improvement. A repeated measures ANOVA was conducted with VAS distress and VAS intensity pre-tDCS and post tDCS as within-subjects variables and condition (frontal tDCS and EEG driven tDCS) as between group variable to verify if there was a significant difference for the responders only on both distress and intensity. We also reported the effect size by including the partial eta squared (η^2).

RESULTS

OVERALL EFFECTS

A comparison between the baseline measurements between the three different groups revealed no significant effect for both tinnitus distress ($F = 0.24$, $p = 0.79$) and tinnitus intensity ($F = 2.01$, $p = 0.13$).

Table 2 | Regions of interest.

Brodmann area	Brain area	Author
BA6	Supplementary motor area	Jastreboff (1990)
BA7	Precuneus	Heller (2003)
BA9-46	Dorsolateral prefontal cortex	Heller (2003), Axelsson and Ringdahl (1989), Baguley (2002), Eggermont and Roberts (2004), Smits et al. (2007), van der Loo et al. (2009)
BA10	Frontopolar cortex	Vanneste et al. (2010a), Muhlnickel et al. (1998)
BA11	Orbitofrontal	Vanneste et al. (2010a)
BA13	Insula	Heller (2003), Weisz et al. (2007)
BA21-22	Secondary auditory cortex	Lockwood et al. (1999), Langguth et al. (2006), Muhlnickel et al. (1998)
BA23-31	Posterior cingulate cortex	Heller (2003)
BA24-32	Dorsal anterior cingulate cortex	Heller (2003), Smits et al. (2007)
BA25	Subgenual anterior cingulate cortex	Heller (2003), Smits et al. (2007)
BA39-40	Angular gyrus	Muhlnickel et al. (1998)
BA41-42	Primary auditory cortex	Lockwood et al. (1999), Langguth et al. (2006), Muhlnickel et al. (1998)

A repeated measures ANOVA revealed a significant main effect for pre versus post measurement ($F = 17.19, p < 0.001, \eta^2 = 0.05$). A closer look to the data indicated that for distress ($F = 25.01$, $p < 0.001$, $\eta^2 = 0.03$) there was a significant decrease in the post tDCS in comparison to pre-tDCS. For intensity a similar effect was obtained ($F = 31.16$, $p < 0.001$, $\eta^2 = 0.04$) demonstrating there was a significant decrease in the post tDCS in comparison to pre-tDCS. No significant main effect was obtained for condition (frontal tDCS, EEG driven tDCS, and waiting list) on both tinnitus distress and tinnitus intensity. In addition an interaction effect was obtained between condition (frontal tDCS, EEG driven tDCS, and waiting list) × tDCS (pre versus post) for both tinnitus distress and tinnitus intensity ($F = 6.59$, $p < 0.001$, $\eta^2 = 0.02$). For tinnitus distress it was shown that both frontal tDCS ($F = 68.73$, $p < 0.001$, $\eta^2 = 0.07$) and EEG driven tDCS ($F = 7.42$, $p < 0.01$, $\eta^2 = 0.04$) had post tDCS a significant reduction in comparison

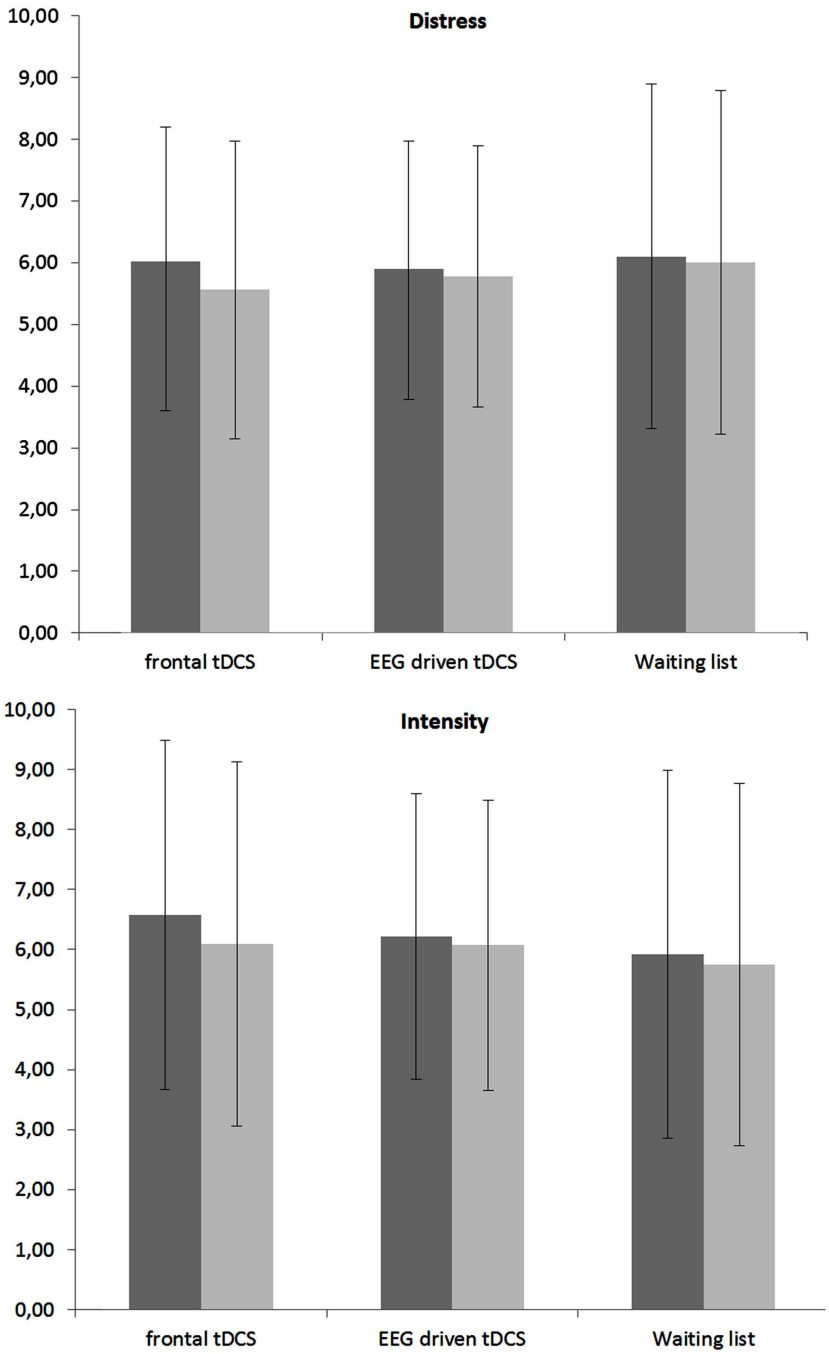

FIGURE 1 | Mean VAS score pre and post tDCS (within-subjects variable) for respectively frontal tDCS, EEG driven tDCS, and a Waiting list group (between-subjects variable) for both tinnitus distress and tinnitus intensity.

to pre-tDCS scores (see **Figure 1**). No effect was obtained for the waiting list group. For tinnitus intensity also a significant decrease was demonstrated post tDCS in comparison to pre-tDCS scores for respectively frontal tDCS ($F = 69.95$, $p < 0.001$,$\eta^2 = 0.09$) and EEG driven tDCS ($F = 9.39$, $p < 0.01$, $\eta^2 = 0.01$). Again, no effect was obtained for the waiting list group. **Figure 1** gives an overview of the obtained results.

A COMPARISON BETWEEN THE EFFECTS OBTAINED FOR FRONTAL AND EEG DRIVEN tDCS

Further analysis indicated a difference for the bifrontal tDCS group for respectively tinnitus distress ($F = 17.72$, $p < 0.001$, $\eta^2 = 0.02$) and tinnitus intensity ($F = 10.74$, $p < 0.01$, $\eta^2 = 0.01$). See **Figure 2** for an overview.

THE EFFECTS FOR RESPONDERS ONLY

If we look what patients respond, we found that bifrontal tDCS in comparison to EEG driven tDCS had a larger response rate for both tinnitus distress ($\chi^2 = 17.03$, $p < 0.001$, $\beta = -0.99$) and tinnitus intensity ($\chi^2 = 10.41$, $p < 0.01$, $\beta = -0.68$). That is, for tinnitus distress 19.2% responded to bifrontal tDCS in comparison to 8.2% for EEG driven tDCS and for tinnitus intensity 22.1% responded to bifrontal tDCS in comparison to 12.5% for EEG driven tDCS.

A repeated measures ANOVA including only the responders on both distress and intensity revealed a significant main effect for pre versus post measurement ($F = 115.22$, $p < 0.001$, $\eta^2 = 0.13$), with a decrease on distress of 36.74% and on intensity of 28.22%. No significant main effect was obtained for condition (frontal tDCS, and EEG driven tDCS) as well for the interaction effect between condition (frontal tDCS, and EEG driven tDCS) × tDCS (pre versus post) for both.

DISCUSSION

The main surprising result of the study is that EEG driven placement of anode and cathode does not benefit tinnitus suppression rates in comparison to bifrontal tDCS with anode overlying the right DLPFC and the cathode overlying the left DLPFC. Even though theoretically one would expect that EEG driven tDCS should be superior to "blind" bifrontal stimulation, this does not seem to be case. Multiple explanations can be proposed.

A first explanation is related to the parameter used. Possibly gamma lagged phase synchronization is not a good parameter to determine where to place the cathode. It has indeed been shown, both in the visual system (Antal et al., 2004) and the DLPFC for tinnitus suppression (Vanneste et al., 2011b) that gamma band activity in the area under the cathode is decreased and increased in the area under the anode. However, it is yet unknown whether this also means that gamma functional connectivity as measured by lagged phase synchronization is also modulated. As tDCS brings neurons closer or further away from threshold depending on the polarity, this should not automatically lead to changes in phase synchronization.

A second possible explanation is that even though gamma band activity is important in tinnitus perception, it has also been proposed that this gamma band activity only leads to conscious perception if this activity is connected to a larger network involved in conscious perception (van der Loo et al., 2009; De Ridder et al., 2011a). Gamma band activity, which normally waxes and wanes, and is spatially restricted to small areas, actually is nested on low

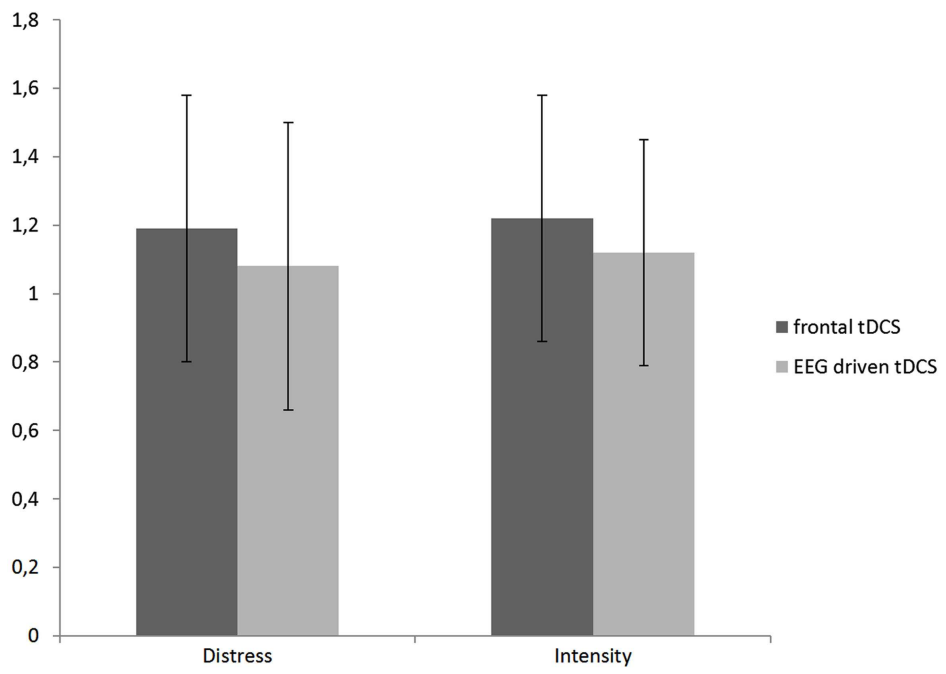

FIGURE 2 | A comparison between the obtained difference (Pre – Post tDCS) for the distress and intensity measurement in respectively frontal and EEG driven tDCS.

frequency activity, predominantly theta activity, in order to connect to widespread larger networks, both for normal cognition (Canolty et al., 2006; Lisman and Buzsaki, 2008) and in tinnitus (De Ridder et al., 2011a). In a recent study it has been demonstrated that auditory attention control is mediated via gamma band activity in different brain areas, which were connected via theta activity, the phase of which determined gamma synchronization (Doesburg et al., 2012). Thus it could have been better to select theta connectivity as a potential prognostic biomarker, as it is possible theta is a carrier wave on which the information rich gamma activity is nested.

Another explanation can be related to the exactness of the electrode positioning. As gamma band activity is usually spatially restricted and only present in a small focal area, the exact positioning of the cathode and anode might be critically involved in the success of the tDCS stimulation. Since this study was not performed using neuronavigation, because of methodological and technical reasons [(1) sLORETA uses standard head model, (2) EEG cannot be read into the neuronavigation machine] it cannot be excluded that the electrodes were not spatially correctly positioned (Vanneste et al., 2011b).

Thus, whereas the results of the bifrontal tDCS seem to confirm previous studies (Vanneste et al., 2010c, 2011b; Faber et al., 2011; Frank et al., 2012), in that bifrontal tDCS with anode overlying the right DLPFC and the cathode the left DLPFC has a beneficial effect on tinnitus loudness and distress perception, the use of gamma band functional connectivity seems not bring any advantage to tDCS for tinnitus suppression. Using other potential biomarkers, such as gamma band activity, or theta functional connectivity could theoretically be better alternatives. Further studies will have to elucidate whether brain state based tDCS has any advantages over "blind" bifrontal stimulation.

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Action mechanisms of transcranial direct current stimulation in Alzheimer's disease and memory loss

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The pharmacological treatment of Alzheimer's disease (AD) is often limited and accompanied by drug side effects. Thus alternative therapeutic strategies such as non-invasive brain stimulation are needed. Few studies have demonstrated that transcranial direct current stimulation (tDCS), a method of neuromodulation with consecutive robust excitability changes within the stimulated cortex area, is beneficial in AD. There is also evidence that tDCS enhances memory function in cognitive rehabilitation in depressive patients, Parkinson's disease, and stroke. tDCS improves working and visual recognition memory in humans and object-recognition learning in the elderly. AD's neurobiological mechanisms comprise changes in neuronal activity and the cerebral blood flow (CBF) caused by altered microvasculature, synaptic dysregulation from ß-amyloid peptide accumulation, altered neuromodulation via degenerated modulatory amine transmitter systems, altered brain oscillations, and changes in network connectivity. tDCS alters (i) neuronal activity and (ii) human CBF, (iii) has synaptic and non-synaptic after-effects (iv), can modify neurotransmitters polarity-dependently, (v) and alter oscillatory brain activity and (vi) functional connectivity patterns in the brain. It thus is reasonable to use tDCS as a therapeutic instrument in AD as it improves cognitive function in manner based on a disease mechanism. Moreover, it could prove valuable in other types of dementia. Future large-scale clinical and mechanism-oriented studies may enable us to identify its therapeutic validity in other types of demential disorders.

Keywords: Alzheimer's disease, cerebral blood flow, frontotemporal dementia, memory loss, network connectivity, neurotransmitter modulation, synaptic and non-synaptic after-effects, transcranial direct current stimulation

INTRODUCTION

As the pharmacological treatment in Alzheimer disease (AD) is limited (Bauer, 2006), alternative therapeutic approaches are worth pursuing, such as non-invasive brain stimulation with transcranial direct current.

Transcranial direct current stimulation (tDCS) is the application of weak electrical currents by saline-soaked surface sponge electrodes to different cortical areas. tDCS can polarity-dependently modulate cortical excitability with prolonged after-effects (Nitsche et al., 2005) and modify neuronal excitability by tonic de-or hyperpolarization of the resting membrane potential (Creutzfeld et al., 1962; Purpura and McMurtry, 1965). The electrode positioning is determined according to the EEG 10–20 system.

tDCS has demonstrated efficacy in improving recognition memory in AD (Boggio et al., 2009, 2011) and it is a useful tool in cognitive neurorehabilitation, as improvements in cognitive functions were described in patients with depression (Fregni et al., 2006), Parkinson's disease (Boggio et al., 2006) and stroke (Monti et al., 2008).

Alzheimer's disease is a progressive neurodegenerative disorder (Thies and Bleiler, 2011) presenting a decrease in acethylcholine activity resulting in cognitive impairment (Schliebs and Arendt, 2011) in many cognitive activities such as memory, language, and executive functions.

The concept of benefiting from modulating cortical excitability via tDCS with consecutive improvement in cognitive functions in AD is thus tempting. We describe tDCS application in clinical studies in patients with dementia (see **Table 1**) and studies on cognitive functions (see **Table 2**) as well as potential underlying mechanisms in this article.

METHODOLOGICAL ASPECTS

The review section about the action mechanisms of tDCS in AD is based on a non-systematic approach, whereas the review section on clinical studies with tDCS in AD and memory is based on a somewhat systematic approach based on the PubMed database. A literature search for original and review articles on tDCS in demential disorders was performed through December 2011 seeking clinical studies on tDCS in AD and for demential disorders, by screening the PubMed database. The keywords were used in combination with "Alzheimer disease" AND "tDCS," "dementia" AND "tDCS" as well as "memory" AND "tDCS." The studies were published between 2004 and 12/2011. The exclusion criteria of articles in the article titles searched were only "brain stimulation," "depression," only "memory" or "Alzheimer disease," or "demential disorder" without "tDCS," "motor learning," and only "tDCS" without "memory" or "Alzheimer disease" or "demential disorder." Thirty-eight papers were screened from 75 articles according to the aforementioned criteria and 33

Table 1 | Clinical studies of tDCS in dementia.

Study	Design	*n*	Age (years)	Disease diagnosis	MMSE	Medication	Parameters	Brain target	Effect
ALZHEIMER'S DISEASE									
Boggio et al. (2009)	Cross over, sham controlled	10	79 ± 9	NINCDS, ADRADA	17 ± 5	AChEIs + others	Anodal/sham, 2 mA, 30 min	Left DLPFC	Improved visual recognition memory after atDCS
Boggio et al. (2011)	Sham controlled	15	78 ± 7, 81 ± 10	Adas-Cog, VRT, VAT, ADAS	21 ± 3, 19 ± 3	No data	Anodal, sham 2 mA, 30 min	TC bilateral	Improved visual recognition memory after atDCS
Ferrucci et al. (2008a)	Cross over, sham controlled	10	75 ± 7	DSM-IV, NINCDS-ADRADA	23 ± 2	AchEI	Anodal/ cathodal/ sham, 1.5 mA, 15 min	Left/right TPC	Accuracy of the word-recognition memory increased after atDCS
FRONTOTEMPORAL DEMENTIA									
Huey et al. (2007)	Double-blind, sham controlled	10	61 (46–80)	Criteria Lund/ Manchester 1994 MDRS	No data	AChEI + memantine	Active/sham, 2 mA, 20 min	FC	No improvement in verbal fluency after active tDCS

AChEI, acetylcholine esterase inhibitors; Adas-Cog, Alzheimer's disease assessment scale-cognitive sub scale; ADAS, Alzheimer's disease assessment scale; DLPFC, dorsolateral prefrontal cortex; DSM- IV, Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV); FC, frontal cortex; MDRS, Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; NINCDS-ADRADA, National Institute of Neurological Communicative Disorders and Stroke-Alzheimer disease and Related Disorders Association; TC, temporal cortex; TPC, temporoparietal cortex; VAT, visual attention task; VRT, visual recognition task.

thereof were used as the basis for the Section "tDCS in Demential Disorders."

tDCS IN DEMENTIAL DISORDERS

ALZHEIMER'S DISEASE

The effect of anodal tDCS (atDCS) over the left temporal cortex (TC) and dorsolateral prefrontal cortex (DLPFC) was investigated on recognition and working memory (WM) in 10 AD patients (Boggio et al., 2009), revealing enhancement in a visual recognition memory task after atDCS of the DLPFC and left TC (Boggio et al., 2009). In another study, an improvement in a word-recognition memory in 10 patients with probable AD was proven after atDCS of the temporoparietal areas (Ferrucci et al., 2008a). In contrast, cathodal tDCS (ctDCS) lead to decreased word-recognition memory. The effect of atDCS persisted up to 30 min after stimulation, indicating a long-lasting increase in brain excitability (Ferrucci et al., 2008a). Long-term enhancement of visual recognition memory for up to 4 weeks after therapy was found after atDCS in 15 AD patients (Boggio et al., 2011).

FRONTOTEMPORAL DEMENTIA

A study demonstrated that active tDCS does not result in a beneficial effect in verbal fluency in 10 patients with frontotemporal dementia presenting mainly behavioral (and in one patient language) symptoms (Huey et al., 2007). The lack of effect may be due to the small current that reaches the frontal cortex due to brain atrophy and neuronal loss with concomitant incapability of the affected cortex to respond to brain polarization (Huey et al., 2007).

SAFETY AND SIDE EFFECTS OF tDCS

General observations

There is evidence that tDCS applied to the scalp over the prefrontal cortex over 20 min does not alter local and global cortical function (Iyer et al., 2005). The current intensity of 1 mA did not result in significant effects on cortical function, whereas verbal fluency increased with 2 mA-atDCS and decreased with 2 mA-ctDCS (Iyer et al., 2005). In a systematic review, itching, tingling, headache, burning sensation, and discomfort were the most often reported adverse effects of active tDCS vs. sham tDCS (Brunoni et al., 2011). Skin irritation and skin burning can occur after tDCS application due to the electrochemical products' skin contact generated by the direct current (Durand et al., 2002; Palm et al., 2008). In addition, magnetic resonance spectroscopy (MRS) in normal subjects failed to detect changes in acetylaspartate, thus showing that atDCS induced no neurotoxic effects (Rango et al., 2008). Furthermore, in motor cortical areas, tDCS induced no relevant changes in serum neuron-specific enolase, a neuronal damage marker, indicating that tDCS induced no harmful effects (Nitsche et al., 2003).

Observations in AD

In studies of tDCS in AD, no adverse effects from tDCS application were noted (Boggio et al., 2009). Only an itching sensation, but no side effects were reported in the study of 10 AD patients (Ferrucci et al., 2008a). No adverse effects, nor tDCS effects on the Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive sub scale (Adas-Cog), or visual attention task (VAT) scores were observed (Boggio et al., 2011).

Table 2 | Studies of tDCS on cognitive functions.

Study	Healthy subjects/ age (age: mean [± standard deviation] or range)	Stimulation electrode	Polarity	Duration/ intensity	Side effects	Effects
Andrews et al. (2011)	10, 20–51 years	Left DLPFC	Anodal/sham	10 min, 1 mA	No	Improvement in a WM task after atDCS
Boggio et al. (2006)	18 Patients with PD, 45–71 years	M 1, left DLPC	Anodal/sham	20 min, 1 or 2 mA	No	Improvement in WM of Parkinson's disease patients after atDCS of the left DLPFC
de Vries et al. (2011)	38, 23 ± 2 years	Broca's area	Anodal/sham	20 min, 1 mA	No	atDCS facilitates the acquisition of grammatical knowledge
Ferrucci et al. (2008b)	13, 75 ± 7 years	Cerebellum	Anodal/cathodal/ sham	15 min, 2 mA	Headache (one patient)	atDCS and ctDCS impairs practice-dependent proficiency in WM
Fiori et al. (2011)	10 Subjects, 3 patients, 45–70 years	Wernicke's area	Anodal/sham	20 min, 1 mA	No	atDCS improved accuracy on the picture-naming task, both normal and patients had a shorter naming latency during atDCS
Flöel et al. (2008)	19, 26 ± 3 years	Cp5	Anodal/cathodal/ sham	20 min, 1 mA	No	Enhanced language learning by atDCS
Flöel et al. (2011)	20, 62 ± 9 years	Right temporoparietal cortex	Anodal/sham	20 min, 1 mA	No	Improved recall one week after learning with atDCS
Fregni et al. (2005)	15, 19–22 years	M1, DLPFC	Anodal/cathodal/ sham	10min, 1mA	No	atDCS leads to enhancement of WM performance
Iyer et al. (2005)	103, 19–70 years	F3	Anodal/cathodal/ sham	20 min, 1 mA	Skin redness	Enhanced verbal fluency by atDCS
Javadi and Walsh (2011)	32, 23 ± 2 years	Left DLPFC, M1	Anodal/sham	20 min, 1 mA	No	Enhancement of verbal memorization after atDCS or impairment of verbal memorization after ctDCS
Kincses et al. (2004)	22, 28 ± 5 years	Fp3	Anodal/cathodal	10 min, 1 mA	No	atDCS enhanced probabilistic classification learning
Marshall et al. (2004)	13, 19–28 years	F3 and F4	Anodal/sham	Alternating 15 s off/15 s on over 30 min	No	atDCS during slow wave sleep improves verbal declarative memory
Marshall et al. (2005)	12, 19–27 years	F3 and F4	Anodal/cathodal	Alternating 15 s off/15 s on over 15 min	No	Impaired performance in WM task by anodal and ctDCS
Ohn et al. (2008)	15, 27 ± 4 years	F3	Anodal/sham	30 min, 1 mA	No	atDCS enhanced performance in a WM task
Penolazzi et al. (2010)	11, 27 ± 5 years	Right F4–C4, Left F3–C3, alternating between atDCS and ctDCS	Anodal/cathodal/ sham	20 min, 1 mA	No	Right atDCS and left ctDCS facilitated the recall of pleasant images regarding pleasant and neutral images
Ross et al. (2011)	14, 55–69 years	Both anterior temporal lobes	Anodal/sham	15 min, 1.5 mA	No	Numerical improvement in face naming after atDCS
Sparing et al. (2008)	15, 27 ± 4 years	Cp5	Anodal/cathodal/ sham	7 min, 2 mA	No	Improved picture naming by atDCS
Teo et al. (2011)	12, 27 ± 9 years	F3 of the DLPFC	Anodal/sham	20 min, 1 mA	No	Current strength may affect WM performance

(Continued)

Table 2 | Continued

Study	Healthy subjects/ age (age: mean [± standard deviation] or range)	Stimulation electrode	Polarity	Duration/ intensity	Side effects	Effects
Zaehle et al. (2011)	10, 25 ± 2 years	Left DLPFC	Anodal/cathodal	15 min, 1 mA	No	Increase in WM performance and amplified oscillatory power in theta and alpha bands after atDCS, interference with WM performance after ctDCS

Abbreviations for electrode placement according to the 10–20 electrode system (Cp5, Cz, Fp3, C3/4: see Recommendations for the practice of clinical. Neurophysiology: guidelines of the International Federation Clinical Neurophysiology. Electroencephalogr. Clin. Neurophysiol. Suppl. 1999;52:1–304), atDCS, anodal transcranial direct current stimulation; min, minutes, ctDCS, cathodal transcranial direct current stimulation, DLPFC, dorsolateral prefrontal cortex; mA, milli Ampere; min, minutes, PD, Parkinson's disease; TPC, temporoparietal cortex.

tDCS IN LEARNING AND MEMORY

OBJECT-LOCATION LEARNING IN THE ELDERLY

The ability to memorize the location of objects is known to worsen by aging and in neurodegenerative dementia. atDCS over the temporoparietal cortex in 20 elderly healthy subjects resulted in improved retention of object-location learning for up to 1 week after learning (Flöel et al., 2011). This finding has relevance concerning memory deficits in normal and pathological aging.

ENHANCING DECLARATIVE MEMORY BY tDCS

Anodal tDCS enhances slow oscillatory EEG activity that in turn can enhance declarative memories (Marshall et al., 2004). As shown in 32 human healthy subjects, declarative memory can be improved by anodal and impaired by ctDCS of the DLPFC (Javadi and Walsh, 2011).

ENHANCING IMPLICIT MEMORY BY tDCS

Both declarative and implicit memory are known to improve via tDCS. For instance, atDCS of Broca's area enhanced implicit learning of an artificial grammar in 38 healthy subjects (de Vries et al., 2011), an interesting finding supporting tDCS as a potential instrument in the rehabilitation of aphasic patients.

MODULATION OF WM BY tDCS

ENHANCING WM BY tDCS

Several studies address the physiological effects of tDCS in the WM as a part of declarative memory playing a pivotal role in long-term memory, language, and executive function (Baddeley, 1992).

In 10 patients with cognitive defects after a first-ever stroke, atDCS of the DLPFC led to enhanced WM performance (Jo et al., 2009). In a neurodegenerative disease like Parkinson's, atDCS of the left DLPFC was also shown to improve WM in 18 patients (Boggio et al., 2006). atDCS to the DLPFC lead to WM enhancement in healthy subjects (Fregni et al., 2005; Andrews et al., 2011) and rats, frontal ctDCS enhanced visual–spatial WM (Dockery et al., 2011). Interestingly, atDCS led to amplified oscillation in theta and alpha electroencephalography (EEG) bands and increased WM performance in humans (Zaehle et al., 2011). WM representations are supported by oscillatory brain activity (Lisman and Idiart, 1995). In particular, theta EEG band activity has been associated with memory encoding and retrieval (Jensen and Tesche, 2002). Thus amplified theta band activity is related to WM's executive function, indicating the continuous information processing required during WM performance.

As neuroimaging studies revealed a widespread effect in cortical activity by tDCS (Lang et al., 2005), it is likely to imply a tDCS influence on the entire WM system, and not only on the DLPFC. Furthermore, there is some evidence that WM performance can be improved in a manner dependent on current strength in 14 healthy subjects (Teo et al., 2011). No current strength or time-course effect was observed in the accuracy of WM tasks. However, a significant current by time interaction was found in a WM task (Teo et al., 2011). However, the effect-dependence on current intensity of tDCS in memory function is not proven by this single study of one WM task; it requires further examination in healthy subjects and those with diverse cognitive functions.

A time-dependent enhancement of verbal memory resulted after atDCS of the DLPFC (Ohn et al., 2008). Name recall can benefit from atDCS of the anterior temporal lobes (Ross et al., 2011), and word retrieval improved in healthy and non-fluent aphasic patients after atDCS (Fiori et al., 2011).

IMPAIRMENT OF WM AFTER tDCS

Bilateral prefrontal ctDCS and atDCS during a memory task can impair neuronal processes related to a WM paradigm (Marshall et al., 2005). Furthermore, cerebellar tDCS of both polarities impaired use-dependent improvement in a WM task (Ferrucci et al., 2008b). WM also revealed impairment by ctDCS to the right parietal lobe (Berryhill et al., 2010).

POTENTIAL MECHANISMS OF ACTION OF tDCS IN AD

EFFECTS OF tDCS ON NEURONAL ACTIVITY BY ALTERING THE MEMBRANE POTENTIAL

In an AD mouse model, ß-amyloid peptide was shown to disturb the resting membrane potential in muscle fibers (Mukhamedi-arov et al., 2011). Furthermore, ß-amyloid 1–42 peptide caused membrane depolarization leading to hyperexcitability of affected neurons in a human neuronal cell model of AD (Blanchard et al., 2002).

atDCS might be an instrument to alter the neuronal depolarization frequently altered in AD according to *in vitro* studies, as atDCS leads to the increased cortical excitability promoting neuronal depolarization (Nitsche and Paulus, 2000). Increasing cortical excitability is a relevant tool in AD, as AD patients reveal temporoparietal hypoactivity (as characterized by focal slow wave activity in magnetoencephalography; Fernandez et al., 2002).

Motor cortex (Di Lazzaro et al., 2004) and global cortical hyperexcitability is found in AD (Rossini et al., 2007), correlating with cognitive severity in a TMS study (Alagona et al., 2001). As ctDCS led to reduced cortical excitability caused by neuronal hyperpolarization (Nitsche and Paulus, 2000), it might also be beneficial in AD by lowering its somewhat increased cortical excitability.

Non-synaptic mechanisms based on changes in the membrane potential underlying the after-effects of atDCS and ctDCS (Ardolino et al., 2005) might be responsible for modulating cognitive function in AD. The local changes in ionic concentrations could be due to alterations in transmembrane proteins and from changes in H+ ions induced by exposure to a constant electrical field (Ardolino et al., 2005).

SYNAPTIC AFTER-EFFECTS OF tDCS

NMDA receptor-dependent after-effects

tDCS induces prolonged after-effects sharing similarities with long-term potentiation (LTP)- and long-term depression (LTD)-like changes in cortical excitability (Paulus, 2004). In an *in vitro* and *in vivo* AD mouse model, LTP as the putative mechanism of learning and memory is evidently impaired by ß-amyloid peptide (Gengler et al., 2010; Middei et al., 2010). ß-amyloid peptide disruption of LTP is *N*-methyl-D-aspartate (NMDA) receptor-dependent in the mouse hippocampus *in vivo* and *in vitro* (Yamin, 2009).

tDCS-induced after-effects are partly NMDA receptor-dependent (Liebetanz et al., 2002), suggesting that tDCS after-effects may alter NMDA receptor-dependent cortical plasticity that may be disturbed in AD.

GABAergic interneurons

Anodal after-effects are probably mediated in part by gamma-aminobutyric acid $(GABA)_A$ergic interneurons as a reduction in short-interval intracortical inhibition and an increase in I-wave facilitation after tDCS intracortical facilitation (Nitsche et al., 2005; Stagg et al., 2009; Stagg and Nitsche, 2011). As in AD, GABAergic cortical inhibitory interneurons play a role in the disease's early stage (Koliatsos et al., 2006); modulation of these interneurons by tDCS is a possible disease-modifying mechanism. Hippocampus changes in GABA B receptor protein were found in 16 elderly subjects with AD, indicating alterations between the excitatory and inhibitory neurotransmitter systems with consecutively dysfunctional hippocampal circuitry (Iwakiri et al., 2005). A MRS study provides evidence that atDCS causes reduced GABA concentration within the stimulated cortex, whereas ctDCS leads to impaired glutamatergic neuronal activity with a correlated reduction in GABA concentration due to a relationship between these two neurotransmitters (Stagg et al., 2009). Thus tDCS might reduce the disequilibrium between excitatory and inhibitory neurotransmitters systems in AD.

Glutamatergic synapses

In AD, glutamate receptors may be dysregulated by ß-amyloid accumulation resulting in the disrupted glutamatergic activity that coincides with cognitive decline (Parameshwaran et al., 2008). The dysregulation of glutamatergic activity might be altered by atDCS, as there is evidence that glutamatergic synapses are involved in anodal after-effects (Stagg et al., 2009; Stagg and Nitsche, 2011), and MRS data support that glutamate and glutamine levels were elevated in the parietal cortex after atDCS (Clark et al., 2011).

Therefore, ctDCS may have the potential to affect cognitive functions in AD by modulating glutamatergic synapses.

EFFECTS OF tDCS ON HUMAN REGIONAL CEREBRAL BLOOD FLOW

There is evidence in AD that characteristics of the cerebral microvasculature have changed, leading to altered cerebral blood flow (CBF; van Beek et al., 2012). atDCS induced an increase in regional cerebral blood flow (rCBF), whereas ctDCS resulted in a decrease in rCBF during and after stimulation (Zheng et al., 2011). As tDCS modulates CBF in many cortical and subcortical regions with sustained and widespread changes in neuronal activity (Lang et al., 2005), it is an auspicious instrument in AD.

MODULATING OSCILLATORY BRAIN ACTIVITY AND FUNCTIONAL CONNECTIVITY PATTERN VIA tDCS

AD led to an altered temporal correlation in parietal and prefrontal oscillations (Montez et al., 2009), more severe deceleration of spontaneous oscillatory activity (Rossini et al., 2007; de Waal et al., 2011), a functional disconnection (Gili et al., 2011), in particular between the prefrontal cortex and hippocampus in AD (Grady et al., 2001), and network connectivity changes (Zhou et al., 2010). It therefore makes sense to use tDCS as a therapeutic tool in AD, as it can reconfigure cerebral networks (Peña-Gómez et al., 2011) and cause changes in functional cerebral connectivity patterns suggesting alterations in brain synchronization (Polanía et al., 2011). As the cognitive dysfunction in brain diseases like AD is based on abnormal neural synchronization (Polanía et al., 2011), it may be beneficial to cause changes in brain synchronization via tDCS.

More specifically, atDCS over the primary motor cortex combined with inhibitory ctDCS of the contralateral frontopolar cortex caused an increased functional connectivity pattern within the premotor, motor, and sensorimotor areas of stimulated hemispheres in 10 healthy human subjects. Furthermore, intra- and interhemispheric connectivity changes became apparent after atDCS, indicating changes in brain topological functional organization (Uhlhaas and Singer, 2006). Another study demonstrated that ctDCS decreased while atDCS augmented normalized beta and gamma frequency EEG bands, suggesting transient reorganization of cortical activity (Antal et al., 2004). As gamma activity is also part of high-level information processing, it is an adjuvant method to influence higher-order cognitive function (Antal et al., 2004).

MODULATING CORTICAL NEUROTRANSMITTERS VIA tDCS

Neuronal loss implicates the impairment of serotonergic neuromodulation as a basic mechanism of promoting dementia in AD (Yang et al., 1999). Furthermore, there is dopaminergic modulation of LTD-like plasticity in AD (Koch et al., 2011). Cholinergic systems with ascending projections are also degenerated in

neurodegenerative dementia (Schmitt, 2005; Fregni et al., 2006). Modulating these neurotransmitter systems via tDCS would therefore seem to be a mechanism-based treatment of AD. Dopaminergic (Nitsche et al., 2006), serotonergic (Nitsche et al., 2009) and cholinergic (Kuo et al., 2007) neuromodulations have been demonstrated by atDCS and ctDCS (Stagg and Nitsche, 2011), indicating another disease-modifying treatment option of tDCS.

There are other mechanisms that determine the response of humans to tDCS, i.e., the BDNF polymorphism (Antal et al., 2004). BDNF modulation is an interesting target in AD, as ß-amyloid processing is involved in the BDNF pathway and (Forero et al., 2006) the BDNF ValMet 66 polymorphism is a neural risk for AD (Voineskos et al., 2011), suggesting BDNF as a factor shaping the cortical excitability response to tDCS in AD patients.

LIMITATIONS OF CURRENT KNOWLEDGE OF tDCS IN DEMENTIAL DISORDERS

There are few studies on the effects of tDCS in demential disorders (AD and frontotemporal dementia, see **Table 1**). The efficacy of tDCS in other demential disorders (for instance vascular dementia or Lewy body dementia) has thus not yet been proven. Furthermore, only a small battery of cognitive functions, i.e., selective attention, WM, visual and word-recognition memory, instruction remembering and word recall has been evaluated so far (see tDCS in Demential Disorders). tDCS effects on other cognitive functions like calculating, cognitive flexibility, language, orientation, short- and long-term memory, and writing will have to be evaluated in studies with larger cohorts and longer control periods. The tDCS effects studied thus far are short-lived (maximum up to 1 month; Boggio et al., 2011) and there are no observations regarding longer-duration interventions. Nor have the long-term side effects of tDCS been assessed. This is particularly important, as tDCS applied over longer periods might interact with mechanisms involved in neurodegeneration with either beneficial (delayed deterioration of cognition) or harmful effects (accelerated cognitive deterioration). The interaction of tDCS with pharmacological treatment has not yet been addressed systematically in studies. However, current data indicate there is no significant interaction between medication outcome and its interaction with tDCS (Boggio et al., 2011).

PERSPECTIVES OF tDCS IN AD

tDCS may enhance our understanding of the neurobiological substrates underlying the cognitive decline in AD. Factors such as cognitive reserve, genetic variants, learning capacity, volumetric studies of cortical thinning and white matter volume, and integrity will have to be thoroughly and systematically investigated in future studies of tDCS on cortical functions in AD. The therapeutic efficacy of tDCS must be examined by outcome scales commonly used in trials of pharmacological agents such as the ADAS-Cog (Freitas et al., 2011). Moreover, multiple target tDCS or tDCS targeting new brain areas must be developed to overcome multiple cognitive deficits in AD. A multi-electrode stimulation set-up was recently demonstrated that increased focalty and intensity at the brain target (Dmochowksi et al., 2011).

CONCLUSIONS

tDCS is an easy to perform and non-invasive alternative therapeutic tool for neurodegenerative diseases such as AD. Its effects comprise the enhancement of cognitive functions in explicit and implicit memory. The mechanisms of tDCS are based on changes in membrane polarization, cerebral blood flow, functional connectivity, and brain oscillatory activity that may be altered in AD and other demential disorders.

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Using transcranial direct current stimulation to treat depression in HIV-infected persons: the outcomes of a feasibility study

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Transcranial direct current stimulation (tDCS) is a novel non-invasive neuromodulatory method that influences neuronal firing rates and excitability of neuronal circuits in the brain. tDCS has been shown to relieve Major Depressive Disorder (MDD) in the general population, suggesting its potential for other vulnerable populations with high MDD prevalence. **Aims:** This study evaluated the feasibility, safety, acceptability, and clinical outcomes of a 2-week tDCS antidepressant treatment in HIV-MDD co-diagnosed patients, and the feasibility of collecting serum and saliva for analysis of immunity biomarkers. **Methods:** Ten enrolled patients underwent baseline evaluation and started the tDCS treatment (Monday–Friday for 2 weeks) delivered with Phoresor II 850 PM for 20 min at 2 mA at each visit, using two saline-soaked sponge electrodes placed over the F3 position of EEG 10–20 system and the contralateral supraorbital region. Outcome measures were collected at baseline, after the last tDCS and 2 weeks later. A quantitative microarray (Ray Bio Tech Inc.) for TH1/TH2 cytokines was used for saliva and plasma analysis. **Results:** Analyzable outcome-data were obtained from eight subjects. Depression scores significantly decreased ($p < 0.0005$) after the treatment. No serious adverse events occurred. Several transient minor AEs and occasional changes of blood pressure and heart rate were noted. Mini-mental state examination scores remained unchanged or increased after the treatment. All subjects were highly satisfied with the protocol and treatment results and described the desire to find new treatments for HIV-MDD as motivating participation. **Conclusion:** Findings support feasibility and clinical potential of tDCS for HIV-MDD patients, and justify larger-sample, sham-controlled trials.

Keywords: transcranial direct current stimulation, HIV, major depressive disorder, neuromodulation

INTRODUCTION

Transcranial direct current stimulation (tDCS) has been shown to be a powerful technique for non-invasive neuromodulation (Nitsche and Paulus, 2010). The primary mechanism of tDCS is a subthreshold modulation of neuronal resting membrane potential which induces a polarity-dependent modification of *N*-Methyl-D-aspartate (NMDA) receptor function (Antal et al., 2010; Nitsche and Paulus, 2010) that plays a role in neuroplasticity. Some of tDCS induced changes occurs immediately during the stimulation (so called intra-tDCS changes), while others occur later as short-lasting or long-lasting after-effects (Nitsche and Paulus, 2010). As suggested by pharmacological studies (Liebetanz et al., 2002; Nitsche et al., 2004), the intra-tDCS effects depend on the activity of sodium and calcium channels but not on efficacy changes of NMDA and gamma-aminobutyric acid (GABA) receptors, and thus are probably generated solely by polarity specific shifts of resting membrane potential. However, the after-effects have been shown to be protein synthesis dependent (Gartside, 1968; Hattori et al., 1990; Nitsche and Paulus, 2010) and also involve modulations of NMDA receptors efficacy. (Liebetanz et al., 2002; Nitsche et al., 2005; Nitsche and Paulus, 2010).

In several randomized controlled studies utilizing 2 or 4 week tDCS treatment protocols, tDCS delivered over the dorsolateral prefrontal cortex (DLPFC) was shown to safely relieve Major Depressive Disorder (MDD) in the general population (Fregni et al., 2006; Boggio et al., 2008a; Rigonatti et al., 2008; Murphy et al., 2009; Nitsche et al., 2009; Kalu et al., 2012). Although the mechanisms of tDCS antidepressant effect are not fully understood, it is reasonable to assume that tDCS might have induced a change in the DLPFC activity which is highly relevant to alterations of mood-related neuronal networks (Boggio et al., 2008a).

This suggests the clinical potential of tDCS treatment for other vulnerable populations with high prevalence of MDD, such as persons with HIV infection. Various estimates (McHorney et al., 1994; Lyketsos, 1995; Boland, 1997; Stober et al., 1997; Chander et al., 2006; Hartzell et al., 2008; Rabkin, 2008) suggest that up to 48% of HIV-infected patients have MDD comorbidity. MDD accelerates HIV disease progression, jeopardizes the completion of antiretroviral treatment and is a potent risk factor for transmission of the virus to others (Wilson et al., 2007). Despite the fact that MDD is the most common psychiatric disorder in HIV populations after substance abuse (Rabkin, 2008), conventional antidepressant treatments, such as medication or psychotherapy, leave many patients with undertreated depressive symptoms (Lyketsos, 1995; Chander et al., 2006; Hartzell et al., 2008). For treatment-resistant depressed patients, depression is often lifelong and disabling and represents a significant source of suffering, disruption in role functioning, economic burden to society, and mortality (Gaynes et al., 2008).

Although tDCS treatment may greatly improve the quality of life of HIV patients suffering MDD, to our knowledge, no previous tDCS study has included such patients. Therefore, we carried out a quantitative and qualitative open-label pilot trial to evaluate the safety, tolerability, acceptability, and clinical outcomes of a 2-week tDCS treatment protocol to treat MDD in HIV-infected patients and explore the feasibility of collecting serum and saliva cytokines for future analysis. The purpose of the study was to determine overall feasibility of the study protocol in an HIV patient-sample and to provide initial data for sample size estimates and power for a future, sham-controlled randomized trial (RCT).

MATERIALS AND METHODS

SUBJECTS

Ten adult subjects diagnosed with HIV and MDD who fully met the following inclusion criteria participated in the study.

Inclusion Criteria comprised of the following: (i) Diagnosed with HIV; (ii) MDD as measured by the Hamilton Depression Rating Scale score at least >17 at the time of enrollment as well as 1 week later at the time of the baseline; (iii) MDD as measured by the Montgomery-Asberg Depression Rating Scale (MADRAS) score at least >11 at the time of enrollment as well as at the baseline.

Subjects were excluded from participation if they met the following exclusion criteria.

Exclusion Criteria: (i) Diagnosed with AIDS; (ii) Active and/or history of schizophrenia, schizoaffective disorder, psychosis, mental retardation, substance dependence, or abuse within the past year (except nicotine), bipolar disorder, psychotic features, amnesic disorder, dementia, delirium, or obsessive-compulsive disorder; (iii) History of opportunistic infection affecting the brain; (iv) Methadone treatment; (v) History of neurological disorder or seizure (except induced by electroconvulsive therapy, ECT), increased intracranial pressure, brain surgery, or head trauma with loss of consciousness for >15 min, implanted electronic device, metal in the head; (vi) History of autoimmune, endocrine, or vascular disorder, unstable cardiac disease, uncontrolled hypertension, or sleep apnea; (vii) Active suicidal intent; (viii) Pregnancy; (ix) Unable to follow instructions or complete assessment tools in English.

Participation in this study did not require any changes in the patient's medication regimen.

PROCEDURES

Overview

The protocol consisted of 12 study visits. At the initial visit, the informed consent was obtained and patients were screened for eligibility. Baseline values of outcome measures were established at the initial visit and 1 week after the initial visit. The subjects who fully met the inclusion criteria then started a 2-week course of tDCS treatment (10 sessions, visits #2 – #11, Monday–Friday for 2 weeks, each session consisting of 20 min of tDCS). Two weeks after the last tDCS treatment, participants came for visit #12 (Follow-up/Completion). The primary outcome measure was safety; secondary outcomes were treatment benefits/clinical outcomes, tolerability, acceptability, and patients' satisfaction. The outcome measurement time points were before the first tDCS treatment, immediately after the last tDCS treatment and at the follow-up visit which was conducted 2 weeks after the treatment.

Transcranial direct current stimulation

Transcranial direct current stimulation was delivered by trained study personnel using the battery-operated device Phoresor II Auto (Model No. PM850) with two saline-soaked sponge electrodes of size 6 cm × 6 cm, with a rubber rim of 1 cm and sponge-skin contact area of 5 cm × 5 cm. The anode was placed over the left DLPFC as determined by the international EEG 10–20 classification (point F3), and the cathode was over the contralateral supraorbital region. The current was delivered at the intensity of 2 mA for 20 min. These parameters of stimulation were successfully and safely used in many previous tDCS studies (Fregni et al., 2006; Rigonatti et al., 2008; Knotkova et al., 2009) and were well within safety limits. A detailed review of tDCS safety and parameters of stimulation-protocols in human subjects appear in Sundaram et al. (2009). The tDCS treatment course was considered complete if the subject received at least 8 of 10 treatment sessions, and if the two missed sessions were not on consecutive days.

Assessment methods

(a) The HamD (*HamD-24)* is the most widely used scale for patient selection and follow-up in research studies of depression treatments. In this clinician-administered instrument, the clinician chooses the best response to each of 24 items by interviewing the patient and by observing the patient's symptoms. Content includes symptoms of depression designated in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; DSM IV-TR) published by the American Psychiatric Association. These include: low mood, insomnia, agitation, anxiety and weight change. The instrument is highly reliable (alpha = 0.87) when the clinician uses the Structure Interview Guide for the Hamilton (SIGH; Williams, 1998) as was done in this study.

(b) The Montgomery-Asberg Depression Rating Scale (*MADRAS*) is a clinician-administered 10-item rating scale to assess the severity of a patient's depressive symptoms within the last 7 days. The items were taken from the 65-item Comprehensive Psychopathological Rating Scale (CPRS) and were selected

because of their sensitivity to change. The 10 selected items are rated on a scale of 0–6 with anchors at 2-point intervals. The interviewer is encouraged to use his or her observations of the patient's mental state as an additional source of information. Total scores on the MADRAS range from 0 to 60. It has been shown to have high inter-rater reliability (Spearman $r = 0.94$) and good concurrent validity (r with HamD between 0.83 and 0.94; Davidson, 1986). We have used this psychometric tool in addition to HamD because MADRAS offers an alternative view of depressive illness, and may be more sensitive than HamD to some depressive symptoms such as hypersomnia, increased appetite, and concentration/indecision.

(c) *Mini-Mental State Examination* (*MMSE*; Folstein et al., 1975) is a widely used clinical instrument for quick detection of cognitive impairment and assessing its severity, as well as for monitoring cognitive changes over time. In this study, MMSE was used as a part of the physical and mental evaluation of subjects at the initial and at the completion visit.

(d) *Patient's Satisfaction Rating Scale* is a combined 4-point (0–3) scale for participants' self-rating when answering the question "How satisfied were you with the results of the tDCS treatment?" 0 = not at all; 1 = a little bit; 2 = a lot; 3 = fully satisfied.

(e) *Patient's Daily Records:* Throughout the study, participants kept at-home daily records (i.e., Daily Diaries) detailing consumption of medications, and potential changes in health status, including depression, pain, fatigue, and level of physical activity.

(f) *Monitoring of the adverse events* (*AEs*) was performed throughout the study using the following: direct contact of study personnel with the participant at study visits, patient's daily diaries, regular phone calls from the study personnel to the patient in the follow-up period. In addition, subjects were instructed to notify the study personnel immediately if any concerns or if any unexpected/sudden changes of health occurred.

(g) *Qualitative Interviews:* Giorgi's phenomenology (Giorgi, 1985) was the method used to describe the experiences of persons undergoing tDCS for treatment of depression. In-person audio-taped interviews were conducted at the completion visit by an experienced qualitative researcher and were immediately transcribed verbatim. Interviews ranged from 30 min to 1 h. Each participant was asked the open-ended question, "Please tell me about your experience undergoing tDCS for the treatment of depression." Probes included the following questions: "What was the experience like for you? What should we continue to do and what should we change to make the experience better for patients?" Themes were derived using the constant comparative method (Thorne, 2000).

Others

One of the study aims was to determine the feasibility of collecting serum and saliva samples for immunity-biomarkers assessment. At the baseline, after the last tDCS treatment, and at the 2-week follow-up visit, approximately 10 ml of plasma and 10 ml of whole stimulated saliva were collected from subjects. Fluid samples were pipetted in to.0 5 ml aliquots and immediately frozen at −80°C, to be prepared for analysis using RayBiotech TH1/TH2 antibody arrays. Results of the analysis will be reported in a separate manuscript (in preparation).

Statistical analysis

To examine change in scores from pre- to post-tDCS administration to 2-week follow-up, we conducted a repeated measures analysis of variance using Predictive Analytics SoftWare (PASW) Statistics, formerly known as Statistical Package for the Social Sciences (SPSS) before it was acquired by IBM. First, analyses determined whether the sphericity assumption was violated for the analysis of the HamD and MADRAS scores. Helmert contrasts were used when comparing (1) the pre-tDCS with the average of the post-tDCS scores and the 2-week follow-up scores, and (2) the post-tDCS scores and the 2-week follow-up scores.

Enrollment and the study procedures took place at Beth Israel Medical Center, New York, NY. Biochemical analysis took place at New York University, New York, NY. The study was approved by the Institutional Review Boards at both institutions.

RESULTS

DEMOGRAPHIC CHARACTERISTICS AND SUBJECTS' FLOW THROUGH THE STUDY

The 10 study participants included 5 males and 5 females. Their mean age was 52.5 (s.d. = 6.3) years, ranging from 38 to 59 years. Almost all (9 of 10) were African American and one was non-Hispanic Caucasian. Five were living with partners/spouses and the others were separated, single, or never married, and living alone. Although five of the participants had attended college, only one was working (and on a part-time basis) and three of the remaining nine were disabled. Scores on the MMSE examination at the baseline were 28.0 (s.d. = 3.1), range 20–30, consistent with the possibility of some mild cognitive impairment for a few of the participants. Regarding their health, the 10 participants had been living, on average, with HIV for 19.7 (s.d. = 4.1) years, range10–26 years. All had co-morbid conditions, including three with hepatitis C virus, three with hypertension, and five with a substance abuse history. All had MDD as reflected in their scores of 17 or greater on the HamD scale; 24.8 (5.8), range 17–34, and a score of 14 or greater on the MADRAS scale: 24.6 (7.4), range 14–34. Before the study, none of the participants had ever had ECT, transcranial magnetic stimulation (TMS), or tDCS treatment for their depression or other reasons. All subjects were taking HIV antiretroviral medication. Besides that, several subjects were on stable regimens of other medications, including the following CNS-acting agents: Antidepressants – selective serotonin reuptake inhibitors [Celexa, Zoloft] (subjects #3,6,9), tetracyclic antidepressants [Remeron] (subject #4), and serotonin-norepinephrine reuptake inhibitors [Effexor] (subject #4); Antipsychotics [Zyprexa, Seroquel, Risperidone] (subjects #4,9); Anticonvulsants [Depakote, Gabapentin] (subjects #4,7); Sedative [Ambien] (subject #9); and Histamine H2-receptor antagonists [Famotidine] (subject #3).

The 10 participants were recruited from a pool of 15 subjects referred to the study. Of these, five were interested in participation but could not participate for various reasons (e.g., could not make commitment to 10 consecutive days of tDCS, lived far away). Ten subjects provided informed consent and were screened according

to the inclusion/exclusion criteria. All 10 subjects satisfied the criteria and began the study protocol. Analyzable outcome-data were obtained from 8 subjects; 7 of them completed all 10 treatments, and 1 subject completed 8 of 10 treatments (missed the last two treatments due to the death of a family member). Two remaining subjects received only two initial treatment sessions and did not continue due to conflicts with their personal schedules.

CHANGES IN DEPRESSION SCALES BEFORE AND AFTER tDCS ADMINISTRATION

Hamilton Depression Rating Scale

Hamilton Depression Rating Scale scores from the eight subjects at baseline, immediately after the last tDCS treatment and at 2-week follow-up averaged 26.3 (s.d. = 5.5), range 17–34; 9.9 (s.d. = 4.3), range 5–17; and 7.6 (s.d. = 6.7), range 1–19, respectively. The mean HamD scores differed significantly between time points according to the repeated measures ANOVA: $F(2, 14) = 94.555$; $p < 0.0005$. The sphericity assumption (see Materials and Methods) was not violated for the HamD scores ($p = 0.926$). As can be seen in **Table 1**, the pre-tDCS HamD scores were significantly higher than the average of the post-tDCS HamD scores and the 2-week follow-up HamD scores [$F(1, 7) = 174.112$; $p < 0.0005$], indicating a highly significant decrease in depression scores.

Notably, the post-tDCS HamD scores did not differ significantly from the 2-week follow-up HamD scores [$F(1, 7) = 2.498$; $p = 0.158$], indicating duration of the decrease of depressive symptoms in the follow-up period.

MADRAS

On MADRAS, scores for the eight patients at baseline, immediately after the last tDCS treatment and at 2-week follow-up averaged 26.8 (s.d. = 6.7), range 14–34; 11.3 (s.d. = 6.9), range 6–26; and 7.0 (s.d. = 7.4), range 0–20, respectively. According to the repeated measures ANOVA, the mean MADRAS scores differed significantly between time points: [$F(2, 14) = 46.490$; $p < 0.0005$]. The sphericity assumption was not violated for the MADRAS scores ($p = 0.421$). As can be seen in **Table 2**, the pre-tDCS MADRAS scores were significantly higher than the average of the post-tDCS HamD scores and the 2-week follow-up MADRAS scores [$F(1, 7) = 59.600$; $p < 0.0005$], indicating a highly significant decrease in depression scores.

The post-tDCS MADRAS scores differed significantly from the 2-week follow-up MADRAS scores [$F(1, 7) = 7.692$; $p = 0.028$], indicating a further decrease in depression scores in the follow-up period.

SAFETY

Safety measures included monitoring side effects throughout the study, systolic and diastolic blood pressure and heart rate before and after each tDCS session, and MMSE at baseline and at the completion of the study.

Side effects

No serious adverse events (SAEs) occurred. Several minor non-serious AEs that occurred during the treatment course or in the follow-up period can be seen in **Table 3**. All these minor events were transient and fully resolved.

Systolic and diastolic blood pressure and heart rate

For each participant, and for each of the 10-days of the tDCS administration, we examined changes in systolic and diastolic

Table 3 | Adverse events presented in the table *in italics* were rated by the study physician as unlikely related or unrelated to the study procedure.

Event	No. of subjects
Unpleasant tingling/prickling sensation under electrode during one tDCS session	2
Mild dizziness	1
Restlessness	1
Swollen/painful ankles	1
Muscle spasm in thigh	1
Worsening of seasonal allergy	1
Disturbed GI (diarrhea and nausea)	1
Tightness in chest due to asthma	1
Pain in left hip	1

Table 1 | Tests of within-subjects contrasts for HAM-D.

Source	Hamilton	Type III sum of squares	df	Mean square	*F*	Sig.
Hamilton	Pre-tDCS vs. Post-tDCS and 2 weeks later	2450.000	1	2450.000	174.112	0.000
	Post-tDCS and 2 weeks later	40.500	1	40.500	2.498	0.158
Error (Hamilton)	Pre-tDCS vs. Post-tDCS and 2 weeks later	98.500	7	14.071		
	Post-tDCS and 2 weeks later	113.500	7	16.214		

Table 2 | Tests of within-subjects contrasts for MADRAS.

Source	MADRAS	Type III sum of squares	df	Mean square	*F*	Sig.
MADRAS	Pre-tDCS vs. Post-tDCS and 2 weeks later	2485.125	1	2485.125	59.600	0.000
	Post-tDCS and 2 weeks later	144.500	1	144.500	7.692	0.028
Error (MADRAS)	Pre-tDCS vs. Post-tDCS and 2 weeks later	291.875	7	41.696		
	Post-tDCS and 2 weeks later	131.500	7	18.786		

blood pressure and heart rate before and after tDCS administration. For systolic and diastolic blood pressure, we considered a change from pre- to post-tDCS administration to be clinically significant if it varied by 10 mmHg or more. For heart rate, we considered a change from pre- to post-tDCS administration to be clinically significant if the change was 10% or greater.

(a) **Clinically significant changes in systolic blood pressure**
For the eight participating patients, clinically significant change in systolic blood pressure varied from −27 to 20 mmHg. All patients had such a significant change on at least one of the days of tDCS administration, ranging from 1- to 5-days. As can be seen in **Table 4**, there were 6 clinically significant increases and 19 clinically significant decreases in systolic blood pressure.
Regarding the days on which the changes occurred, they included a change for one of the patients on each of days 6 and 9; for two patients on days 1, 3, 5, and 8; for three patients on days 2 and 10; for four patients on day 7; and for five patients on day 4.

(b) **Clinically significant changes in diastolic blood pressure**
For the eight participating patients, clinically significant change in diastolic blood pressure varied from −20 to 15 mmHg. Six of the eight patients had such a significant change on at least one of the days of tDCS administration, ranging from 1- to 5-days. As can be seen in **Table 4**, there were five clinically significant increases and 10 clinically significant decreases in diastolic blood pressure. Regarding the days on which the changes occurred, they included no changes for any patients on day 2; changes for one patient on days 5, 6, 9, and 10; for two patients on days 1, 3, 7, and 8; and for three patients on day 4.

(c) **Clinically significant changes in heart rate**
Each of the eight evaluated subjects had at least 1 day on which there was a clinically significant change in heart rate, ranging from 1- to 5-days. There were nine clinically significant increases and 14 clinically significant decreases in heart rate (**Table 4**). Regarding the days on which the changes occurred, they included change for one patient on days 2, 5, 9, and 10; for two patients on days 3 and 6; for three patients on days 7 and 8; for four patients on day 1; and for five patients on day 4.

Mini-mental state evaluation before and after treatment

Scores for the eight subjects on the MMSE ranged from 20 to 30 (mean = 28; s.d. = 3.02) before the tDCS treatment and from 25 to 30 (mean = 29.0; s.d. = 1.8) at the follow-up. The individual participant scores remained either unchanged or increased after the treatment. There was no case of the score-decrease between the baseline and the end of the study assessment.

ADHERENCE TO THE TREATMENT

Adherence to the treatment was determined as the percentage of participants who finished the 2-week tDCS treatment course, and the percentage who completed the entire study, including participation in the 2-week follow-up. Only two subjects (20%) did not receive the minimum of required eight tDCS treatment sessions. Each of the two subjects completed two treatment sessions at the beginning of the treatment course. Both subjects dropped out due to a personal-schedule conflict and did not come for the follow-up evaluation.

Eight subjects (80% of patients) received the required eight or more treatment sessions. Of these, six subjects did not miss any treatment sessions, one subject missed one treatment, and one subject missed two treatments. As the two missed treatments (last two treatments of the course) for this latter subject were on consecutive days, the subject as per protocol did not finish the treatment course and was not considered a completer. However, all other data and evaluations were collected from this subject and included in the analysis. Qualitative evaluation of this non-completer revealed that the subject missed the two sessions due to the death of family member. The subject's frequent communication with the study personnel revealed high motivation to participate in the study procedures and exhibited behavior typical for treatment-adherent subjects. If this non-completer is eliminated from the analysis, there were very few substantial changes in study results. In particular, as was the case with the eight participants, the pre-tDCS HamD scores were significantly higher than the average of the post-tDCS HamD scores and the 2-week follow-up HamD scores for the seven completers [$F(1, 6) = 137.388$; $p < 0.0005$]. In addition, the pre-tDCS MADRAS scores were significantly higher for the seven completers than the average of the post-tDCS MADRAS scores and the 2-week follow-up MADRAS scores [$F(1, 6) = 72.199$; $p < 0.0005$]. For the seven completers,

Table 4 | Clinically significant change from pre- to post-tDCS administration in systolic[a] and diastolic blood pressure[a] and heart rate[b].

	Subject #2	Subject #3[c]	Subject #4	Subject #5	Subject #6	Subject #7[d]	Subject #9	Subject #10	Total
No. of days of systolic BP increase	2	2	0	1	0	0	1	0	6
No. of days of systolic BP decrease	3	2	2	1	4	4	2	1	19
No. of days of diastolic BP increase	1	0	2	0	1	0	0	1	5
No. of days of diastolic BP decrease	1	1	3	0	3	0	1	1	10
No. of days of heart rate increase	0	0	3	0	2	0	4	0	9
No. of days of heart rate decrease	2	2	1	1	1	3	1	3	14

[a] *A change of 10 mmHg is considered clinically significant.*

[b] *A change of 10% is considered clinically significant.*

[c] *Data on systolic and diastolic blood pressure and heart rate were missing on Day 3.*

[d] *Data on systolic and diastolic blood pressure and heart rate were not collected on Days 9 and 10 as the subject did not come for the two study visits.*

analyses also indicate duration of the decrease in depressive symptoms from immediately post-tDCS to the 2-week follow-up on both the HamD and the MADRAS. However, although there was a statistically significant further decline in depressive symptoms as measured by the MADRAS when the eight participants were included in the analysis [$F(1, 7) = 7.692$; $p = 0.028$], the decline on the MADRAS was only of borderline significance when only the seven completers were included [$F(1, 6) = 5.250$; $p = 0.062$].

PATIENTS' SATISFACTION

Patient's scores on the 4-point (0–3) Satisfaction numerical rating scale after the last tDCS session as well as at the follow-up ranged between 2 (satisfied a lot with the results of tDCS treatment) and 3 (fully satisfied). After the last tDCS, six of eight subjects were fully satisfied with the results, and two subjects were satisfied a lot, mean score 2.75, s.d. 0.46. At the 2-week follow-up, seven subjects were fully satisfied and one subject was satisfied a lot, mean score 2.88, s.d. 0.35, indicating that the level of satisfaction with the results of the tDCS treatment did not deteriorate during the post-treatment follow-up period.

PRELIMINARY FINDINGS FROM QUALITATIVE INTERVIEWS

Four themes emerged to describe participants' experiences with tDCS: (a) a narrative of frustration and helplessness with previous depression and medication treatment, (b) the sensory experience of tDCS, including tingling at site placement and desensitization to tingling or irritation after the first few treatments, (c) altruism, with particular attention to improving depression treatment for other HIV-infected persons, and (d) clearer thinking with reduced perseveration, rigidity of thinking, and drug cravings.

Subjects who did not complete the treatment indicated a high motivation to participate in the entire study but said that unanticipated scheduling conflicts prevented them from doing so. They each suggested that future tDCS treatment protocols be developed to maximize flexibility for participants (i.e., offering options of evening and weekend appointments so that subjects could "make up" a missed session). The subject who received eight sessions of tDCS said she was noting improvement in her mood and clarity in her thinking. The other two non-completers who received two treatment sessions did not perceive any changes in depressive symptoms. The interviews did not reveal any identifiable differences in the demographic or clinical characteristics of subjects who completed the treatment compared with non-completers. All 10 participants reported their willingness to participate in future tDCS clinical trials.

FEASIBILITY OF BIOMARKER-COLLECTION

All study participants agreed to provide samples of blood and saliva for biochemical analysis of immunity biomarkers. At the time of collection, all subjects fully cooperated and followed instruction of study personnel. Data collection of serum and saliva samples for cytokine assays was feasible in this patient population.

DISCUSSION

This was a pilot, open-label study to determine the feasibility of using novel tDCS antidepressant treatment in HIV-infected persons. The study evaluated clinical outcomes, safety, acceptability, and patient's satisfaction with the treatment, as well as the feasibility of collecting serum and saliva cytokine biomarkers in a 2-week tDCS treatment protocol.

To our knowledge, this is the first study to provide evidence about the feasibility of the tDCS treatment protocol in an HIV population, and the first tDCS study applying a mixed methods approach.

In accordance with the previous tDCS studies in the general population (Fregni et al., 2006; Boggio et al., 2008a; Rigonatti et al., 2008; Kalu et al., 2012), the results of our study showed a decrease of depressive symptoms after tDCS treatment. Although our study was not sham-controlled, the relief of depressive symptoms was well beyond effects attributable solely to placebo response observed in previous studies (Fregni et al., 2006; Boggio et al., 2008a; Rigonatti et al., 2008; Kalu et al., 2012). Further, it is of great clinical interest that the improvement of depressive symptoms after tDCS in our study did not deteriorate in the 2-week follow-up period, which provides a rationale for future studies of durability of tDCS effects.

Further, results of our study contributed to evidence on the safety of tDCS treatment, as none of our subjects experienced any SAE; the few non-SAEs that occurred in our study were minor and transient. Monitoring and evaluation of blood pressure and heart rate before and after each tDCS session showed occasional bi-directional changes in these parameters. The changes were not specific to the study participants with a history and/or present status of hypertension, and a decrease of the parameters was observed more often than an increase. Of note, numerous factors could contribute to the observed changes, including anticipation stress prior the first tDCS stimulation, physical activity immediately prior the study visit, or level of relaxation during the 20-min "quiet time" when receiving tDCS stimulation. The decreasing effect of tDCS on blood pressure has been previously noted and Cogiamanian et al. (2010) discussed the potential use of tDCS in the treatment of hypertension. However, our finding of bi-directional fluctuation suggests caution and monitoring of blood pressure and heart rate during tDCS stimulation, and further studies of tDCS effects.

A gratifying finding in our study was the high adherence of subjects to the study protocol. It could be partially because our study subjects were completers of an NIH-funded study of HIV patients (R01 AI070005, ACT 2, PI M.V. Gwadz; Gwadz et al., 2011) that educated patients on relevant issues concerning research participation to facilitate minorities' access to participation in suitable research trials. The high adherence in our study not only supports feasibility of the 2-week tDCS treatment protocol and its use in a future RCT, but also contributes to evidence of validity of the ACT 2 educational intervention.

The findings from the qualitative evaluation of the semi-structured interviews at the end of the study revealed high satisfaction with the study and willingness of all subjects to participate in future tDCS studies. The findings were consistent with previously reported (Rosedale et al., 2009) patients' experiences with the repetitive transcranial magnetic stimulation (rTMS) treatment; participants described intense frustration and helplessness with previous depression and medication treatment, arguing for novel treatment approaches (Rosedale et al., 2009). The theme of electrode placement, tingling, and desensitization to tingling

or irritation after the first few treatments has been previously described in the rTMS, but not in the tDCS literature (Anderson et al., 2006). Altruism has not been previously described as a motivating factor for participation in brain stimulation studies and may have been a particular feature of the ACT 2 group participants or a particular motivating factor for persons infected with HIV.

Clearer thinking with reduced perseveration, reduced rigidity of thinking, and reduced drug cravings have been previously described in the tDCS literature and suggest that tDCS may enhance acute attention and working memory in people with depression (Loo, 2012). Notably, attention-enhancement as well as reduced cravings for specific foods and alcohol has also been observed in patients treated with tDCS (Boggio et al., 2008b; Fregni et al., 2008; Kang et al., 2009). This may present enormous clinical opportunity for the HIV patients who present with high comorbidity of substance abuse.

Our results also support feasibility of saliva and blood sample collection for the immunity-biomarker analysis and indicate an applicability of this procedure in future RCT tDCS protocols involving HIV-infected subjects.

The major limitations of the study and its findings are (i) the small sample size that limits generalizability of the results, (ii) the open-label design of the study, (iii) the trained clinical raters were not blinded to the study protocol, (iv) the study have not used parallel versions of MMSE at the post-treatment re-testing, and therefore an order effect might have contributed to the MMSE results. As the study was not sham-controlled, a future RCT is warranted before conclusions on effectiveness of tDCS antidepressant treatment in an HIV population can be drawn.

CONCLUSION

The study demonstrated feasibility of the 2-week tDCS treatment protocol in HIV-infected patients, as well as the feasibility of study enrollment and satisfactory retention of the subjects which supports future tDCS studies in this patient population.

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A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression

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Objectives: Transcranial direct current stimulation (tDCS) has demonstrated some efficacy in treatment-resistant major depression (TRD). The majority of previous controlled studies have used anodal stimulation to the left dorsolateral prefrontal cortex (DLPFC) and a control location such as the supraorbital region for the cathode. Several open-label studies have suggested effectiveness from anodal stimulation to the left DLPFC combined with cathodal stimulation to the right DLPFC. Thus, this study evaluated the efficacy of tDCS using anodal stimulation to the left DLPFC and cathodal stimulation to the right DLPFC compared to sham tDCS. **Methods:** Subjects between the ages of 18 and 65 were recruited from a tertiary care university hospital. Twenty-four subjects with TRD and a 17-item Hamilton Rating Scale for Depression greater than 21 were randomized to receive tDCS or sham tDCS. The rates of remission were compared between the two treatment groups. **Results:** The remission rates did not differ significantly between the two groups using an intention to treat analysis. More subjects in the active tDCS group had failed a course of electroconvulsive therapy in the current depressive episode. Side effects did not differ between the two groups and in general the treatment was very well tolerated. **Conclusion:** Anodal stimulation to the left DLPFC and cathodal stimulation to the right DLPFC was not efficacious in TRD. However, a number of methodological limitations warrant caution in generalizing from this study. Ongoing, controlled studies should provide further clarification on the efficacy of this stimulation configuration in TRD. ClinicalTrials.gov Identifier: NCT01078948.

Keywords: depression, transcranial direct current stimulation, treatment-resistance, clinical trial

INTRODUCTION

Major Depressive Disorder (MDD) is a highly prevalent mental illness (Kessler et al., 2003; Patten et al., 2006). Despite the vast number of pharmacological and psychotherapeutic treatments that are available, as many as 50% of patients fail to respond to treatment (Pincus and Pettit, 2001; Sackeim, 2001; Fava, 2003). In addition, the pharmacological augmentation and combination strategies frequently used in treatment-resistant depression (TRD) often increase the risk of adverse events and drug interactions (Joo et al., 2002; Dew et al., 2007; Papakostas, 2008). Electroconvulsive therapy (ECT) has demonstrated superior efficacy outcomes in TRD (Eranti et al., 2007; Lisanby, 2007). However, many patients are reluctant to engage in a trial due to stigma and the risk of cognitive adverse effects (Lisanby, 2007). The need for alternative treatment strategies to optimize outcomes for patients who experience TRD has been recognized as one of the future directions for addressing this disorder (Insel, 2006).

Transcranial direct current stimulation (tDCS) is a non-invasive and non-convulsive form of brain stimulation in which a weak, direct current (typically 1–2 mA) is applied using two surface scalp electrodes. Initial studies in animals suggested that such stimulation could elicit polarity-dependent alterations in cortical excitability and activity, with anodal stimulation increasing cortical excitability and cathodal stimulation causing cortical inhibition (Bindman et al., 1964). Furthermore, these resultant changes were not limited solely to the period of stimulation, but endured for minutes to hours afterward (Bindman et al., 1964). More recently, Nitsche and Paulus (2001) demonstrated that comparable changes occurred following tDCS directed to the human motor cortex, providing further evidence of its neuromodulatory potential.

As a result of its capacity to alter cortical activity, investigators in the 1960s began to investigate tDCS as a possible treatment for depression (Costain et al., 1964; Lippold and Redfearn, 1964; Redfearn et al., 1964); however, results were mixed, methodological differences between studies confounded results, interest in pursuing tDCS waned and the development of pharmacological antidepressant agents dominated the ensuing decades. Since the 1990s, however, research in various forms of invasive and non-invasive brain stimulation such as deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation (rTMS) has been re-invigorated. A resurgence of interest may be partially a consequence of the recognition that, despite advances in pharmacotherapy, treatment-resistance remained a persistent issue in the treatment of depression (Fava, 2003; Rush et al., 2006).

In spite of renewed interest in examining tDCS as a potential treatment for major depression, its efficacy, as well as its optimal stimulation parameters, have yet to be established. A recent meta-analysis that reviewed 10 studies (six of which were randomized controlled trials) reported that compared to sham tDCS, active tDCS was more effective in reducing symptoms of depression (Kalu et al., 2012). The authors caution, though, that the small number of studies hindered their meta-analysis, many of which had limited sample sizes, eligible for inclusion. A large, randomized sham-controlled trial that used anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC) and cathodal stimulation over the contralateral supraorbital region showed a significantly greater improvement in depression scores in subjects receiving active tDCS compared to sham over a 3-week controlled phase, although differences in response or remission criteria were not demonstrated. However, after an additional 3 weeks in an open-label extension phase, those subjects who had received active stimulation were significantly more likely to achieve a 50% reduction in symptoms (Loo et al., 2012).

Although the pathophysiology and etiology of major depression is complex, one hypothesis underlying a number of brain stimulation studies is that there exists a pathological aberration and imbalance in the activity of the left and right prefrontal cortices, with the left DLPFC hypoactive and right DLPFC overactive in those with depression (Baxter et al., 1989; Fitzgerald et al., 2008; Grimm et al., 2008). With the aim of ameliorating this putative imbalance between the two hemispheres, many brain stimulation studies attempt to enhance the excitability of the left DLPFC while dampening the activity of the right prefrontal cortex (Fitzgerald et al., 2006; Blumberger et al., 2011). Though there is much debate in the ECT literature regarding the efficacy of unilateral and bilateral treatment, it is clear that both forms of stimulation involve widely distributed neurobiological change as a consequence of seizure generalization (Nobler et al., 2001). A recent brain imaging study has demonstrated that tDCS can produce electrode dependent changes in regional brain activity in the prefrontal cortex (Merzagora et al., 2010). Thus, there is a rationale for directing anodal tDCS over the left DLPFC, while placing cathodal stimulation over the right DLPFC.

The optimal placement of the electrodes remains under investigation – several tDCS studies, using bilateral frontal stimulation that resulted in an improvement of depressive symptoms, have positioned the cathode over the right supraorbital region rather than over the right DLPFC (Fregni et al., 2006a; Boggio et al., 2008; Loo et al., 2010). Moreover, as regions other than the prefrontal cortices have also been implicated in depression, it may be prudent to explore the effects of alternative electrode montages on the efficacy of tDCS. Another recent open-label, pilot study used fronto-extracephalic stimulation, in which anodal stimulation was directed over the right DLPFC and cathodal stimulation was directed over the right, upper arm (Martin et al., 2011). The subjects had previously participated in a tDCS trial that delivered bifrontal stimulation and subjects experienced the two treatment groups consecutively. The authors reported a 43.8% reduction in depression scores with a more rapid response when compared to bilateral frontal stimulation.

The relationship between degree of symptom severity and treatment-resistance is intrinsic to the question of efficacy of tDCS treatment. Many earlier studies that demonstrated promising results, included individuals experiencing mild to moderate depression and did not necessitate that participants meet criteria for treatment-resistance (Fregni et al., 2006a; Boggio et al., 2008; Rigonatti et al., 2008). Several, open-label studies have suggested that left DLPFC cathodal and right DLPFC anodal tDCS may be an effective treatment configuration in more severely depressed patients (Ferrucci et al., 2009; Brunoni et al., 2011a; Dell'Osso et al., 2011). Thus, the current study was designed to determine the efficacy of tDCS providing both left and right DLPFC stimulation using anodal and cathodal stimulation respectively. We hypothesized that this electrode placement configuration would lead to greater improvement compared to sham, with a larger effect size than previous unilateral approaches with anodal stimulation of the left DLPFC and cathodal stimulation over the supraorbital region. In addition, we hypothesized that tDCS would be as tolerated as well as sham stimulation with minimal side effects.

METHODS

SUBJECTS

Twenty-four outpatients (20 female, 4 male; mean age 47.3 years, range 24–62) were recruited from the Mood and Anxiety, Geriatric Mental Health, and Brain Stimulation Treatment and Research programs at the Centre for Addiction and Mental Health (a tertiary university teaching hospital) as well as via referrals from physicians in Ontario, Canada. All subjects had a diagnosis of unipolar Major Depressive Disorder without psychotic features and were experiencing a Major Depressive Episode, as confirmed by the Structured Clinical Interview for the DSM-IV (SCID-IV). Subjects were required to have a score of $\geq$21 on the 17-item Hamilton Rating Scale for Depression (HRSD-17). Subjects were required to meet stage II criteria on the Thase Scale for treatment-resistance (failure to achieve remission or inability to tolerate two trials of an antidepressant from separate classes; Thase and Rush, 1995). Concomitant medications, such as various classes of antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants), benzodiazepines, and antipsychotics were permitted provided that subjects had been on a stable dose of their medications for at least 4 weeks prior to entering the study and were able to maintain those stable dosages for the duration of the protocol. Subjects taking anticonvulsants were ineligible for the study, as certain agents have been found to disrupt the effects of anodal tDCS (Nitsche et al., 2003). Moreover, individuals were not included in the study if they: (i) had a DSM-IV history of substance abuse or dependence in the 6-months prior to enrolling in the study; (ii) had a concomitant, major and unstable medical, or neurologic illness; (iii) had a history of seizures; (iv) were pregnant; and/or (v) met DSM-IV criteria for borderline personality disorder or antisocial personality disorder based on the SCID for DSM-IV Axis II Disorders (SCID-II). The research ethics board at the Centre for Addiction and Mental Health approved the study and all subjects provided written, informed consent prior to commencing their involvement in the trial.

STUDY DESIGN AND TREATMENT

Following completion of baseline clinical measures, subjects were randomly assigned using a computer-generated randomization list with the information stored on a centralized computer to receive either active or sham tDCS. Only the treating clinician was aware of subjects' treatment condition. Fifteen treatments, each lasting 20 min, were administered over the course of 3 weeks (one treatment per weekday) with clinical raters and subjects blind to treatment group allocation. After receiving seven treatment sessions, subjects were assessed using the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) and continued with the remainder of their treatment course, whereupon they were reassessed with the full clinical rating battery and the blind was broken. During the informed consent process, subjects were told that there were two treatment conditions (i.e., active or sham stimulation) and were instructed not to discuss their treatment experiences with the clinical rater.

At the time of the study design, there was no data on the bilateral electrode placement proposed. However, we postulated that 46 patients would be required to have a 80% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 8 in the sham group to 15 in the active tDCS group. We planned an interim analysis at the midpoint of the trial.

TREATMENT PROTOCOL

Transcranial direct current stimulation treatment was delivered using a battery-operated, constant current stimulator (CX-6650; Rolf Schneider Electronics, Germany) and transmitted by two rubber electrodes ($7\text{ cm} \times 5\text{ cm} = 35\text{ cm}^2$), each covered by a saline-soaked sponge and affixed to the head with a headband. The anode was directed over the left DLFPC and the cathode was placed over the right DLPFC, corresponding to electrodes F3 and F4, respectively, according to the 10–20 EEG system. Neuronavigation studies (Herwig et al., 2001) have indicated that this is a reasonably accurate method of locating the DLPFC, and it has also been used in previous tDCS studies targeting the DLPFC (Fregni et al., 2005, 2006a). In the active treatment group, stimulation was delivered at 2 mA for 20 min; sham stimulation was delivered using parameters identical to those in the active condition with the exception of the stimulator being programmed to turn off after 30 s, allowing the investigators to mimic the initial somatic sensations experienced with active tDCS, but without providing putative therapeutic benefits (Gandiga et al., 2006; Ambrus et al., 2010). In both treatment arms, the stimulator was oriented in such a way that subjects were unable to view the settings of the treatment parameters on the front panel of the machine. Subjects were permitted to make up missed treatments; however, they were not allowed to miss more than four treatments over the duration of the study.

CLINICAL ASSESSMENTS

Experienced clinical raters blind to treatment assignment administered the following rating scales at baseline and post-treatment: the MADRS, HRSD-17 (Hamilton, 1967), the Brief Psychiatric Rating Scale (Overall and Gorharn, 1962), and the Beck Depression Inventory (BDI; Beck et al., 1961). Subjects underwent an abbreviated assessment at the trial midpoint (i.e., after seven treatments) consisting of the MADRS only.

OUTCOME MEASURES

The primary outcome for the study was change from baseline to endpoint on the HRSD-17. All subjects were assessed at baseline, at the point of early treatment termination, if possible, and after 15 treatments. Secondary outcomes included remission (score ≤ 7) and response (50% improvement). Other measures included change from baseline to endpoint, as well as response and remission on MADRS and BDI-II.

DATA ANALYSIS

All statistical analyses were conducted using statistical software (SPSS for Windows 15.0; SPSS Inc., Chicago, IL, USA) and the analysis was conducted on an intention to treat basis. Baseline differences in demographic and clinical variables were compared between treatment groups. Continuous variables were analyzed with one-way analysis of variance (ANOVA). Categorical variables were analyzed with a two-tailed Fisher's exact test (for dichotomous comparisons). All procedures were two-tailed and we used a significance level set at $\alpha = 0.05$ for the primary outcome. Analysis of the primary outcome was performed using repeated measures ANOVA.

RESULTS

PARTICIPANT FLOW, FOLLOW-UP, AND SAMPLE CHARACTERISTICS

Of 47 patients screened, 4 did not meet eligibility criteria and 19 declined participation. A total of 24 patients were randomized (see **Figure 1**).

The subjects' baseline clinical and demographic characteristics are summarized in **Table 1**. There were no clinically important differences between groups. Nineteen subjects were taking antidepressant medication (with or without other agents) during the trial. There were no differences in the proportion of subjects taking any of the medication classes. Six subjects in the tDCS group and two subjects in the sham group had received treatment with ECT in previous depressive episodes. Three subjects in the tDCS group and one in the sham group had failed a course of ECT during the current depressive episode. Post-treatment (week 1) data on the primary outcome measure was available for $n = 21$ subjects (87.5%). Subjects who were lost to follow-up did not differ from retained subjects on any of the baseline clinical, cognitive, or demographic variables. Nineteen subjects received all 15 treatments, of the remaining five subjects the number of missed treatments were 14, 12, 4, 1, 7 respectively. Of a total of 19 subjects who were assessed for maintenance of the blind, 14 subjects (73.7%) correctly guessed whether they received active or sham treatment: 6 (60.0%) in the active tDCS group and 8 (88.9%) in the sham group. These proportions did not differ significantly between the two groups ($p = 0.30$). The blinding of clinical raters was not assessed.

PRIMARY OUTCOME: CHANGE IN HRSD-17

The mean post-HRSD score in the active tDCS group and sham stimulation group are shown in **Table 2**. There was no difference in HRSD change between the two groups ($F = 0.063$; $\text{df} = 1$; $p = 0.80$). The same analysis was run for all subjects who completed all 15 treatments. Similarly, there was no difference in HRSD change between the two groups ($F = 0.30$; $\text{df} = 1$; $p = 0.59$). None of the subjects in either group met criteria for remission on the

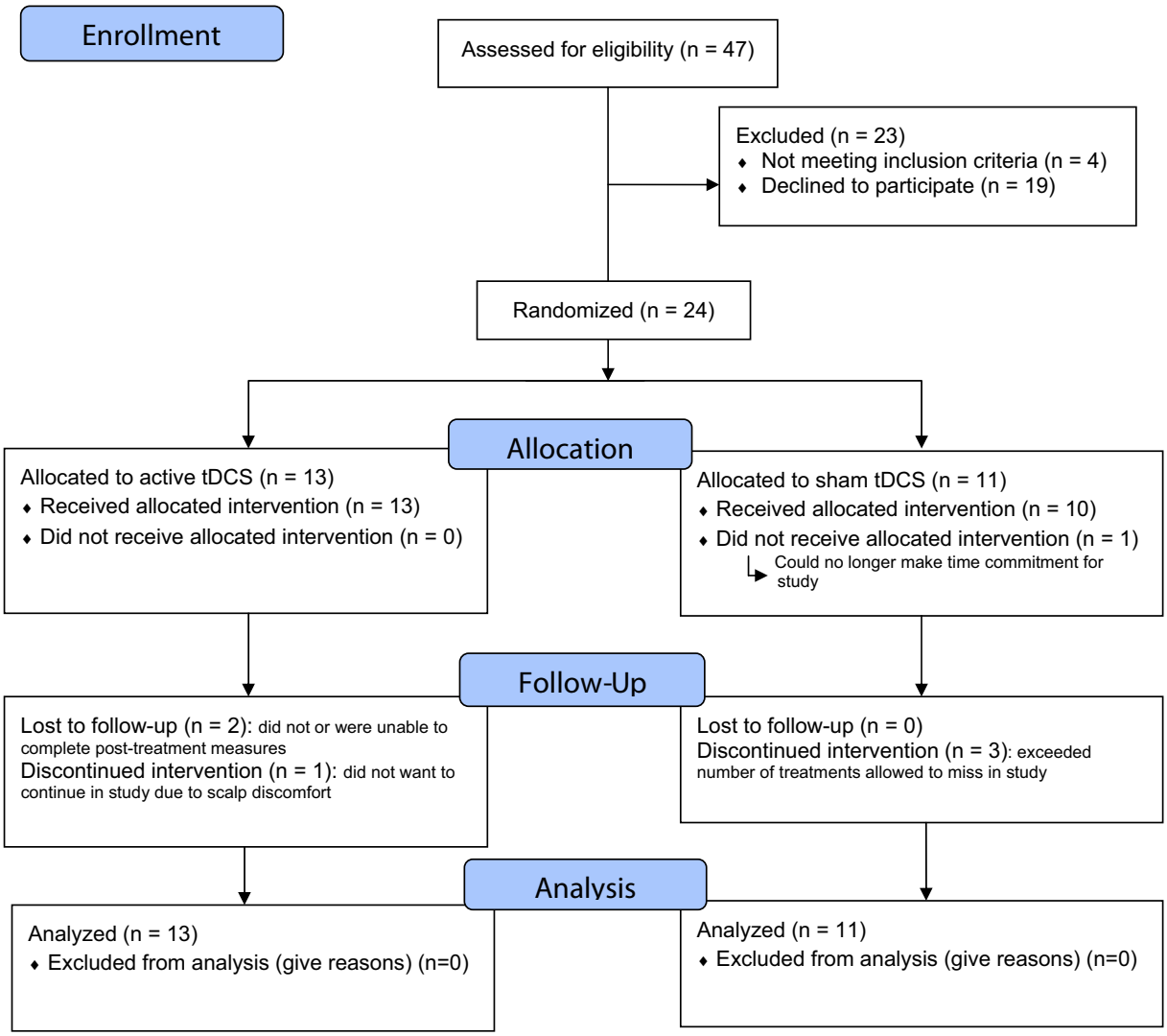

FIGURE 1 | CONSORT flow chart of the study. The study was registered at URL: http://clinicaltrials.gov/show/NCT01078948 (ID:NCT01078948).

HRSD. One subject in each group met criteria for response on the HRSD (Fisher's exact $p = 1.00$).

SECONDARY OUTCOME MEASURES

Montgomery-Asberg depression rating scale

The mean post-MADRS score in the active tDCS group and sham stimulation group are shown in **Table 2**. There was no difference in MADRS change between the two groups ($F = 0.38$; df = 1; $p = 0.55$). One of the subjects in the active tDCS group achieved response (Fisher's exact $p = 1.00$) and remission criteria (Fisher's exact $p = 1.00$) while no subjects met response or remission criteria in the sham stimulation group.

Beck depression inventory-II

The mean post-BDI-II score in the active tDCS group and sham stimulation group are shown in **Table 2**. There was no difference in BDI-II change between the two groups ($F = 1.1$; df = 1; $p = 0.38$). Two of the subjects in the active tDCS group and one in the sham stimulation group achieved remission criteria (Fisher's exact $p = 1.00$). Three subjects in the active tDCS group and one in the sham stimulation group met criteria for response (Fisher's exact $p = 0.58$).

ADVERSE EFFECTS AND TOLERABILITY

As indicated, 3/24 subjects (28%) did not complete an endpoint assessment for the primary outcome: 2/13 in the active tDCS group and 1/11 in the sham group (see **Figure 1**). Three subjects had an endpoint assessment but did not receive all 15 treatments as they missed too many sessions and were withdrawn. Four subjects in the sham group reported mild skin tingling. Two subjects in the active group reported mild skin tingling and two reported mild to moderate skin tingling. Three subjects in the active group reported mild headache while no subjects reported headache in the sham group. No serious adverse events were reported during the trial. One subject in the sham group withdrew due to scalp discomfort.

Table 1 | Demographic and baseline clinical characteristics.

Characteristic	tDCS ($n = 13$)	Sham ($n = 11$)
DEMOGRAPHICS		
Age, years (mean, SD)	45.3 (11.6)	49.7 (9.4)
Gender, M/F	3/10	1/10
One or more medical illnesses	9 (69.2)	6 (54.5)
DEPRESSION HISTORY		
Recurrent episodes (%)	13 (100)	9 (81.8)
Current episode severe (%)	1 (7.7)	0 (0)
Current episode moderate (%)	12 (92.3)	11 (100)
Atypical features (%)	1 (7.7)	1 (9.1)
Melancholic features (%)	1 (7.7)	1 (9.1)
Comorbid anxiety (%)	4 (30.8)	1 (9.8)
Number of depressive episodes (mean, SD)	2.9 (2.3)	3.8 (3.7)
Duration of current episode in years (mean, SD)	4.3 (5.6)	3.4 (3.0)
Baseline HRSD (mean, SD)	24.9 (3.1)	24.1 (2.9)
Baseline MADRS (mean, SD)	31.5 (5.8)	32.0 (7.0)
Baseline BDI-II (mean, SD)	35.4 (8.1)	36.4 (6.8)
Baseline BPRS (mean, SD)	32.0 (3.3)	31.4 (3.7)
TREATMENT HISTORY		
SSRI (%)	2 (15.4)	2 (18.2)
SNRI (%)	7 (53.8)	2 (18.2)
Tricyclic antidepressant (%)	2 (15.4)	1 (9.1)
Mirtazapine (%)	1 (7.7)	2 (18.2)
Bupropion (%)	4 (30.8)	3 (27.3)
Antipsychotic augmentation (%)	1 (7.7)	1 (9.1)
Med combination (%)	9 (69.2)	8 (72.7)
Benzodiazepine Use (%)	6 (46.2)	2 (18.2)
History of ECT (%)	6 (46.2)	2 (18.2)
ECT failure in the current episode (%)	3 (23)	1 (9.1)
No antidepressant (%)	2 (15.4)	3 (27.3)
Number of failed antidepressant trials (mean, SD)	4.3 (2.4)	4.1 (2.2)

Table 2 | Primary and secondary outcome measures (mean, SD) at baseline and post-treatment.

	Baseline		Post-treatment	
PRIMARY OUTCOME				
HRSD-17 scores	tDCS ($n = 13$)	sham ($n = 11$)	tDCS ($n = 13$)	sham ($n = 11$)
	24.9 (3.1)	24.1 (2.9)	18.8 (4.77)	18.1 (5.5)
SECONDARY OUTCOMES				
MADRS scores	31.5 (5.8)	32.0 (7.0)	25.4 (5.2)	27.7 (6.4)
BDI-II scores	35.4 (8.1)	36.4 (6.8)	23.0 (13.8)	26.4 (8.6)

DISCUSSION

To our knowledge this is the first randomized sham-controlled trial comparing tDCS that employed anodal stimulation to the left DLPFC and cathodal stimulation to the right DLPFC. We did not find any differences between the efficacy of active and sham stimulation. Both treatment groups improved over the 3-weeks of the trial. Overall, the treatment was well tolerated with only one subject withdrawing due to scalp discomfort.

The strengths of this study included focus on inclusion of treatment-resistant subjects with stage II or higher treatment-resistance (Thase and Rush, 1995), the use of sham tDCS as a control, and an increase in the number of treatments to 15 over 3 weeks (longer than most previous treatment trials).

A number of potential limitations may explain the lack of efficacy from active tDCS in the current study. The most important limitation is the small sample size of the study. Despite the clear lack of separation between the two conditions, it is possible that differences may have been demonstrated had the study continued to its anticipated sample size of 46. Given the lack of differences between groups and the interim analysis we felt that continuing the study would not be ethical. Though we sought to include patients with treatment-resistance, the level of treatment-resistance may have been too high to observe an effect. Indeed, a third of the sample in the active stimulation group had failed a course of ECT in the current episode and nearly half had ECT in previous episodes. Though the number of subjects who failed a course of ECT in the active tDCS group was not statistically different from the number that failed a course of ECT in the sham group, the active group may have been biased toward non-response due to the small numbers in the study. Failure of ECT has generally been an exclusion criterion in other brain stimulation trials (Fregni et al., 2006b; O'Reardon et al., 2007; George et al., 2010). Future controlled trials should ensure that subjects with excessively high levels of treatment-resistance are characterized and accounted for in the randomization by stratification or excluded from the eligibility criteria. Another major limitation of the study is the high overall correct guess of treatment condition in the study. The correct guess rate calls into question the adequacy of the blinding and thus the sham control in this study. However, the sham procedure in the current study followed the directions and recommendations of previous studies (Gandiga et al., 2006; Ambrus et al., 2010). Equal numbers of subjects in both the sham and active group reported skin tingling suggesting that the sham was effective at providing a somatic sensation. However, more subjects in the active group reported headache and more intense skin tingling. It is possible that the treating technician gave non-verbal cues to subjects indicating treatment condition, however, we have no way of assessing whether this occurred. Though medication initiation was controlled in this study, the possibility remains that subjects who started an antidepressant immediately before study entry may have experienced a delayed response (i.e., greater than 4 weeks) to their antidepressant during the trial (Rush et al., 2003). However, the majority of subjects, who were taking an antidepressant, had been on stable doses of medication for longer than 8 weeks. Furthermore, the variability in the use of any antidepressant may have impacted the effect of the treatment. The use of benzodiazepines by patients may have also limited the efficacy of the treatment as this class of medication has been shown to impair the neurophysiological effects of stimulation (Nitsche et al., 2004). A greater percentage of patients in the active stimulation group were taking benzodiazepines. In addition, the patients in the active group had a longer duration of illness and had failed more medication trials. Collectively, these

differences suggest that the active stimulation group were more treatment-resistant.

Notwithstanding these limitations, it is concerning that we did not demonstrate differences on any of the primary or secondary outcome measures. None of the subjects in the study met criteria for remission on the HRSD-17-item. A recent meta-analysis has also concluded that the effects of tDCS are somewhat muted (Kalu et al., 2012). A more recent randomized, double-blind, sham-controlled study in patients who had failed to respond to at least two previous trials of antidepressants from different classes did not find a difference between active left DLFPC and right supraorbital stimulation and sham stimulation of 2 weeks duration (Palm et al., 2012). Subjective ratings on secondary outcome measures, such as the Positive and Negative Affect Scale, suggested that active tDCS was associated with an increase in positive emotions and also trended toward a decrease of negative emotions (Palm et al., 2012). The largest study of tDCS in depression has recently been reported and though there was a significant difference in the change of MADRS scores, there was no difference in responders and remitters between active and sham stimulation (Loo et al., 2012). The authors suggested that longer treatment durations up to 6 weeks might be necessary to achieve clinical response with tDCS (Loo et al., 2012). We hypothesized that providing excitatory stimulation (anode) to the left DLPFC and inhibitory stimulation (cathode) to the right DLPFC would lead to improved efficacy. The theoretical rationale for this comes from the ECT literature and some previous rTMS studies showing improved efficacy with excitatory stimulation to the left DLPFC and inhibitory stimulation to the right DLPFC (Fitzgerald et al., 2006; Blumberger et al., 2011). However, recent data has not replicated the finding of improved efficacy with this stimulation pattern (Fitzgerald et al., 2012). Furthermore, it is possible that the montage of left and right DLPFC were too close together leading to shunting over the scalp. While it may be theoretically advantageous to stimulate bilaterally, the physical properties of tDCS may not be amenable to this electrode placement.

A series of three open-label trials have suggested that the stimulation technique used in this study is an effective form of tDCS in the treatment of depression (Ferrucci et al., 2009; Brunoni et al., 2011a; Dell'Osso et al., 2011). One study showed a 30% improvement in depression rating scale scores in 14 inpatients with a severe major depressive episode using twice daily treatments. Similarly, the other two studies found positive effects in both unipolar and bipolar depressed patients after 10 treatments over 5 days (Brunoni et al., 2011a; Dell'Osso et al., 2011). In contrast, we did not find this stimulation configuration to be more beneficial than sham stimulation when providing treatment once daily. However, we would caution generalizing from the current study due to the limitations identified. The design of the Sertraline vs. ELectrical Current Therapy (SELECT) tDCS trial will utilize the same stimulation parameters as the current study and should provide greater clarification regarding the efficacy of anodal stimulation to the left DLPFC and cathodal stimulation to the right DLPFC (Brunoni et al., 2011b).

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CLINICAL CASE STUDY
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Immediate effects of tDCS on the μ-opioid system of a chronic pain patient

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We developed a unique protocol where transcranial direct current stimulation (tDCS) of the motor cortex is performed during positron emission tomography (PET) scan using a μ-opioid receptor (μOR) selective radiotracer, [^{11}C]carfentanil. This is one of the most important central neuromechanisms associated with pain perception and regulation. We measured μOR non-displaceable binding potential (μOR BP_{ND}) in a trigeminal neuropathic pain patient (TNP) without creating artifacts, or posing risks to the patient (e.g., monitoring of resistance). The active session directly improved in 36.2% the threshold for experimental cold pain in the trigeminal allodynic area, mandibular branch, but not the TNP patient's clinical pain. Interestingly, the single active tDCS application considerably decreased μORBP_{ND} levels in (sub)cortical pain-matrix structures compared to sham tDCS, especially in the posterior thalamus. Suggesting that the μ-opioidergic effects of a single tDCS session are subclinical at immediate level, and repetitive sessions are necessary to revert ingrained neuroplastic changes related to the chronic pain. To our knowledge, we provide data for the first time *in vivo* that there is possibly an instant increase of endogenous μ-opioid release during acute motor cortex neuromodulation with tDCS.

Keywords: tDCS, PET, opioid receptors, neuroplasticity, trigeminal neuropathic pain, post-herpetic neuralgia

BACKGROUND

Pain is described as a complex experience affecting not only the sensory, but also the affective and cognitive systems (Merskey and Bogduk, 1994). Although the central mechanisms involved in pain perception and modulation have not been completely elucidated, recent years have seen significant advances in the understanding of the anti-nociceptive mechanisms controlling the pain experience in humans. One of the most important modulatory mechanisms is the endogenous opioidergic system, which is involved in the regulation of experimental and clinical pain, as well as in the effects of analgesic opiate drugs. Studies with positron emission tomography (PET) have shown decreased opioid receptor non-displaceable binding potential (BP_{ND}) in patients with chronic pain disorders, including rheumatoid arthritis (Jones et al., 1994), neuropathic pain (Maarrawi et al., 2007a; DosSantos et al., 2012), and fibromyalgia (Harris et al., 2007) when examined with both selective for μ-opioid receptor (μOR; Harris et al., 2007; DosSantos et al., 2012) and non-selective (Jones et al., 1994; Maarrawi et al., 2007a) opioid receptor markers. The data available points to either or both endogenous opioid release, and down-regulation of opioid receptors. It has also been demonstrated that sustained pain activates μOR mediated neurotransmission in a complex network of brain areas related to pain, including the dorsolateral prefrontal cortex, anterior cingulate, anterior and posterior insula, thalamus, hypothalamus, amygdala, and periaqueductal gray matter. Furthermore, the magnitude of these regional activations was related to the individual's capacity to suppress sensory and affective elements of the pain experience (Zubieta et al., 2001).

Therapies that directly modulate brain activity in specific neural networks might be particularly suited to relieve chronic pain. Interestingly, a novel method of non-invasive brain stimulation, namely transcranial direct current stimulation (tDCS), has been reported to produce lasting therapeutic effects, when applied to the motor cortex, in chronic pain disorders, including fibromyalgia (Fregni et al., 2006; Riberto et al., 2011), orofacial pain attributed to viral infection (Antal and Paulus, 2011), and chronic migraine (DaSilva et al., 2012). This technique is based on the application of a weak direct current to the scalp that flows between two electrodes (anode and cathode). Some studies have shown that the efficacy of tDCS depends critically on parameters such as electrode position and current strength (Nitsche et al., 2003). In fact, application of tDCS for 13 min to the motor cortex can modulate cortical excitability for several hours (Nitsche and Paulus, 2000, 2001). Two cortical areas have been explored in pain studies using tDCS: primary motor cortex and dorsolateral prefrontal cortex (Nitsche et al., 2008; DaSilva et al., 2011). In the most common setup for pain research the anode is positioned over the motor cortex (M1) and the cathode over the supra-orbital area (DaSilva et al., 2011). It has been described that the cortical excitability can be changed up to 40% with this method (DaSilva et al., 2011). Regarding the specific area stimulated in M1, studies with non-invasive brain stimulation have shown better results for

facial pain with the stimulation of the hand cortical area (medially located) and more significant improvement of hand pain when the cortical area representing the face (more laterally located) is stimulated. One possible explanation would be the direct effect of tDCS/TMS on the thalamus, which could lead to stimulation of the ventroposteromedial nucleus (VPM), responsible for the nociceptive input from the face (Lefaucheur et al., 2004, 2006; Lefaucheur, 2006).

CASE PRESENTATION

SUBJECT

A 62-year-old woman was recruited by the Headache and Orofacial Pain Effort (H.O.P.E.) laboratory at the University of Michigan to participate in an ongoing study investigating the effects of the tDCS in the μ-opioidergic system. She had a history of herpes zoster in 2008, with severe pain, affecting the distribution of the left ophthalmic (V1) and maxillary (V2) divisions of the trigeminal nerve. The pain persisted after the complete healing of the initial lesions, leading to a diagnosis of post-herpetic neuralgia. During the baseline evaluation, she described the pain as constant, spontaneous, throbbing, aching, heavy, and hot-burning. The average pain intensity was four out of ten and the average of the unpleasantness associated with the spontaneous pain was six out of ten. The pain was alleviated by sleep and massage and aggravated by sleepiness, stress, and alcohol. The patient reported eye dryness and nasal congestion related to her pain. The symptoms could not be triggered with heat, cold, touch, or chewing. Her pain was not associated with nausea, vomiting, photophobia, or headache. The patient rated the levels of social interaction (0 = isolation, 10 = social gathering), attention (0 = inattention, 10 = high awareness), and anxiety (0 = least, 10 = most) at two, three, and six out of ten, respectively, during the spontaneous pain. She had been treated with amitriptyline 10 mg once a day and pregabalin 50 mg twice a day, with only partial control of her pain. The scores of the McGill Pain questionnaire (MPQ) descriptors during the baseline evaluation were: 24 (sensory), 5 (affective), 2 (evaluative), and 7 (miscellaneous). The pain rating index (PRI) was 38 and the present pain intensity (PPI) was three (distressing). All procedures reported were carried out in accordance with the bioethical rules for studies involving human beings of the WMA (World Medical Association, 2012) – Declaration of Helsinki (2008). The protocol of this study was previously approved by the University of Michigan Investigational Review Board for Human Subject Use and by the Radioactive Drug Research Committee of the US Food and Drug Administration. The patient gave written informed consent prior to the participation in the study.

NEUROIMAGING

We used a radiotracer with specific affinity for μORs, [^{11}C] carfentanil. The participant underwent one baseline and one tDCS90-min PET scan using a Siemens (Knoxville, TN, USA) HR + scanner in 3D mode (reconstructed images have a full-width at half maximum (FWHM) resolution of approximately 5.5 mm-in-plane and 5.0 mm axially). Synthesis of high specific activity [^{11}C]carfentanil (>2000 Ci/mmol) was produced by the reaction of [^{11}C]methyliodide and a non-methyl precursor (Dannals et al., 1985; Jewett, 2001). Each [^{11}C]carfentanil dose (10–15 mCi, ≤0.03 μg/kg) was administered at 50% as a bolus with the remnants constantly injected across the session to reach normalized tracer levels approximately 35 min after tracer administration.

Positron emission tomography images were reconstructed using interactive algorithms into a 128 × 128 pixel-matrix in a 28.8 cm diameter field of view (FOV). Twenty-eight image frames were obtained and co-registered to one another. They were corrected for motion and decay (Minoshima et al., 1993). Dynamic image data for each scan were converted on a voxel-by-voxel basis into two sets of parametric images: First, a tracer transport measure (K1 ratio) used for co-registration and normalization procedures; and second, a receptor-related measure, distribution volume ratio (DVR, equal to $B_{max}/K_d + 1$ or binding potential at equilibrium (BP_{ND}) + 1). These two measures were estimated using a modified Logan graphical analysis using the occipital cortex as the reference region (Logan et al., 1996).

A T1-weighted anatomical MRI scan was acquired on a 3 T scanner (General Electric, Milwaukee, WI, USA). The MRI acquisition utilized the following sequence parameters: axial spoiled-gradient recalled (SPGR) 3D acquisition, 15.63 bandwidth, repetition time [TR] = 9.2 ms, echo time [TE] = 1.9 ms, inversion recovery preparation 500 ms, flip angle = 15°, 25/26 FOV, number of excitations [NEX] = 1, 144 contiguous slices, 1.0 mm slice thickness, 256 × 256 matrix.

Images were anatomically standardized into template space using Statistical Parametric Mapping (SPM8) software by (A) co-registering the MR scan and K1 scans; (B) normalizing the MR scan to the Montreal Neurologic Institute (MNI) template brain using DARTEL; and (C) applying the resulting deformation matrix to the PET images. Co-registration and normalization accuracy was verified by comparing the transformed MR and PET images to the MNI atlas template.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Both placebo and active tDCS were applied during the second PET scan. The placebo tDCS was applied during the early phase of the exam (15–35 min), while the active tDCS during the late phase (60–80 min). This sequence was adopted to avoid carry-over effects from the placebo tDCS. In active stimulation 2 mA of tDCS was applied for 20 min. The anode was placed over the area corresponding to the primary motor cortex (M1) while the cathode was positioned over the supra-orbital region. For placebo tDCS, the same method was used; however current was applied only for 30 s. This has been demonstrated to be a reliable method of sham stimulation (Gandiga et al., 2006) as sensations arising from tDCS treatment are observed usually at the beginning of application. The impedance was controlled under 5 kΩ during the whole period of active stimulation to avoid abnormal increase of the overall resistance and consequently heat that could potentially burn the patient. The tDCS protocol used in this study is fully explained in a stepwise manner by our scientific team in DaSilva et al. (2011). Due to the space restrictions, considering the stimulation inside the PET scanner, a special system was developed to add more solution to the sponges when needed. This system consisted of two syringes, each one connected to one sponge by two small tubes. Each electrode was positioned inside a 35 cm^2 sponge, that was soaked with approximately 12 mL of saline solution (6 mL per

side) before the PET and up to 12 mL during the procedure. We used saline solutions with lower concentrations of NaCl (15 mM) (DaSilva et al., 2011).

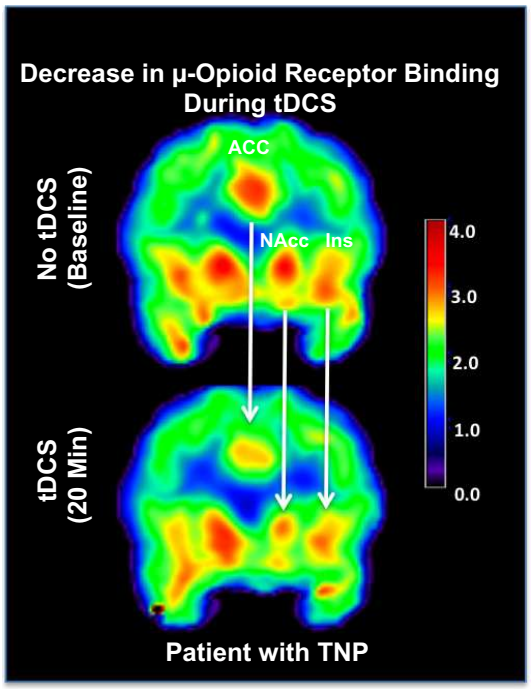
QUANTITATIVE SENSORY TESTING

In this study we controlled the effects of tDCS on the thermal perception as assessed by the Quantitative Sensory Testing (QST) in three moments during the second PET: before starting the scan, in the period between sham and active tDCS (approximately 40–60 min) and after the scan. For this purpose, a QST protocol, consisting of thermal pain thresholds for cold and hot stimuli, was performed using a Thermal Sensory Analyzer TSA 2001-II (Medoc, Israel) (Yarnitsky and Sprecher, 1994; Bachmann et al., 2010). The thermal stimuli were applied upon V3, bilaterally, and dorsal radial area of both hands. Each stimulus was applied for three consecutive times and the average was calculated.

RESULTS

Levels of μOR BP_{ND} in our trigeminal neuropathic pain patient (TNP) patient during a single tDCS application immediately induced significant decrease in μOR binding in many (sub)cortical pain-matrix structures, including nucleus accumbens (NAc), anterior cingulate cortex (ACC), insula (Ins), and thalamus (Thal; **Figures 1** and **2**). For instance, the M1-tDCS montage considerably decreased μOR binding in the posterior thalamus (R: 21.5%; L: 19.54%), compared to sham tDCS (R: 2.2%; L: 4.7%).

No significant changes were observed in the clinical pain levels related to tDCS. The pain as assessed by the visual analog scale (VAS) was four out of ten before the second PET, three after placebo tDCS, and returned to four after the PET. Regarding the QST, a significant increase in the temperature for heat threshold was observed in the left V3 after sham tDCS and when comparing baseline and active tDCS. On the hand, the temperature for cold threshold showed a significant decrease in the left V3 after active tDCS but not after placebo tDCS. When comparing the cold threshold after active tDCS to the baseline threshold (before starting the PET scan), there was a reduction of the temperature at which cold pain was detected in the left V3 of approximately 36.2%. Significant changes in the heat and cold thresholds associated with sham and active tDCS were also observed in other regions, such as right V3, and right hand. The QST results are presented in the **Table 1**.



Global Values: Baseline, 1.56; tDCS, 1.48
(4.5 % difference)

FIGURE 1 | Decrease in μ-opioid receptor binding associated with transcranial direct current stimulation. Upper panel: μOR BP_{ND} during the baseline PET. Lower panel: μOR BP_{ND} during active tDCS. ACC, anterior cingulate cortex; NAc, nucleus accumbens; Ins, insula.

DISCUSSION

To our knowledge, this is the first study showing an immediate reduction in theμOR binding in response to an acute motor cortex neuromodulation, suggesting that the analgesic effect of M1-tDCS is possibly due to direct increase of endogenous opioid release.

Endogenous opioid systems have long been implicated in regulating pain nociceptive signals, with μORs being the primary mediators of opiate analgesia, but also the rewarding and tolerance-producing effects of opiates (Sora et al., 1997). Both elements, endogenous opioid release and μOR concentrations, are therefore critical elements for the understanding of chronification and alleviation of pain in TNP patients. The first direct evidence of regional endogenous μ-opioid activation during sustained experimental trigeminal pain in healthy humans was published by Zubieta et al. (2001) using PET, measured with external imaging as reductions in the *in vivo* availability of μORs BP_{ND} quantified with [^{11}C]carfentanil. Acute reductions in μOR BP_{ND} were observed in the PAG, thalamus, hypothalamus, NAc, ventral pallidum, amygdala, insula, and dorsal anterior cingulate (dACC), correlating with suppression of sensory and affective qualities of the pain challenge.

The investigation of the response of the endogenous opioid system to TNP and its neuromodulation models is of importance to understand the mechanisms in place to regulate the pain experience. This information is key to better predict the varied responses of TNP patients to therapeutic interventions. Jones et al. (1994, 1999) utilized [^{11}C]diprenorphine, a non-selective opioid radiotracer, to examine the *in vivo* availability of opioid receptors in a small group of patients diagnosed with rheumatoid arthritis and trigeminal neuralgia before and 3 weeks to 3 months after treatment and pain relief. Substantial reductions in cortical and subcortical opioid receptor availability were observed prior to treatment at resting state (baseline), which were reversed after pain relief. Similar results were obtained with [^{11}C]diprenorphine in four central post stroke pain patients and in a patient with a pontine infarction and pain (Willoch et al., 1999, 2004), suggesting a dysregulation of central opioid mechanisms at baseline in response to chronic pain, regardless of pain etiology. Interestingly, in a study with eight refractory neuropathic

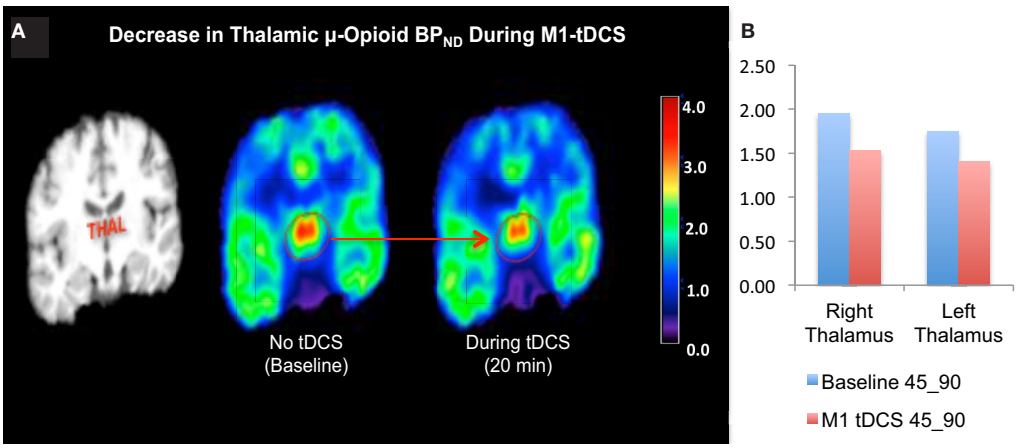


FIGURE 2 | (A) Decreased thalamic μ-opioid receptor availability during active tDCS, represented in the coronal plane. **(B)** Bar chart illustrating the μ-opioid receptor binding potential in the right and left thalamus during the late phase of the first and second PET scans.

Table 1 | Variations in the heat and cold thresholds related to placebo and active tDCS.

Region	Heat/ cold	Before PET		After placebo tDCS		After active tDCS		Significance level (*p*)		
		Mean	SD	Mean	SD	Mean	SD	Baseline × placebo tDCS	Baseline × active tDCS	Placebo × active tDCS
Left V3	Heat	35.8	0.4	42.7	1.9	44.9	0.9	***p* < 0.001**	***p* < 0.001**	*p* > 0.05
Right V3	Heat	42.2	0.8	43.6	1.1	44.1	1.1	NS	NS	NS
Left hand	Heat	46.3	1.0	46.3	1.0	43.5	2.1	NS	NS	NS
Right hand	Heat	44.2	1.0	40.0	1.1	44.2	1.9	***p* < 0.05**	*p* > 0.05	*p* > 0.05
Left V3	Cold	23.7	2.3	22.7	2.5	15.1	3.2	*p* > 0.05	***p* < 0.05**	***p* < 0.05**
Right V3	Cold	20.1	3.8	20.2	3.8	9.5	5.9	*p* > 0.05	***p* < 0.05**	***p* < 0.05**
Left hand	Cold	15.1	6.8	18.3	6.8	12.9	4.3	NS	NS	NS
Right hand	Cold	14.1	3.4	12.6	2.3	18.0	9.1	NS	NS	NS

Statistical significance (in bold) was defined at p < 0.05 (one-way ANOVA followed by Tukey's test).

pain patients, postoperative (invasive) motor cortex stimulation induced decreases of [^{11}C]diprenorphine binding in the anterior mid-cingulate cortex (MCC) and PAG, which were significantly correlated with pain relief (Maarrawi et al., 2007b). The authors suggested that the decrease in binding of the exogenous ligand was possibly due to receptor occupancy by enhanced release of endogenous opioids. This analgesic mechanism is highly associated with M1 cortex stimulation, at least with rTMS, since it is blocked with naloxone injection (Taylor et al., 2012). tDCS over M1 induces immediate changes in thermal sensory percepts in health subjects, especially cold (Bachmann et al., 2010). In addition, it produces long lasting pain relief in chronic pain patients, including TNP (Lima and Fregni, 2008). Recently, it was reported that acute tDCS modulates functional connectivity depending on its polarity (Polania et al., 2011). Anodal stimulation over M1 with contralateral frontocortical cathode placement (our protocol) immediately increases functional coupling between ipsilateral M1 and thalamus. On the contrary, cathodal tDCS over M1 decreases functional coupling between ipsilateral M1 and contralateral putamen.

The findings above hint why the anode M1/cathode orbitofrontal electrode montage results in optimal modulation of pain-matrix hyperactivity, specially the thalamus, which underlies chronic pain. Here, in our case report data with TNP, the same active M1-tDCS montage considerably decreased μOR binding in the posterior thalamus (**Figure 2**). Nonetheless, it is possible that an additional opioid release might have been prevented by a potential carry-over effect related to the sham stimulation.

Remarkably, the single tDCS application immediately improved 36.2% the threshold for experimental cold pain in the allodynic V3 area (baseline: 23.7°C ± 2.3; placebo tDCS: 22.7°C ± 2.5; active tDCS 15.1°C ± 3.2), but not the TNP patient's clinical pain (baseline: 4, VAS 0-10); placebo tDCS: 3; active tDCS: 4). Suggesting that the immediate opioidergic effects of a single tDCS session are subclinical, and repetitive sessions are necessary to revert ingrained neuroplastic changes related to the chronic TNP suffering (see next paragraph). This is in agreement with the results from multiple clinical tDCS studies, showing a

direct relationship of patients' clinical pain improvement with the number of tDCS sessions (Lima and Fregni, 2008).

CONCLUDING REMARKS

This case report represents a change of paradigm, as we directly modulated the same opioid mechanisms under study by applying novel neuroimaging and neuromodulatory tools. Future studies are necessary to confirm our results, and to investigate further the effects of tDCS on the endogenous opioid system in a larger cohort of patients.

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Enhancing motor skill learning with transcranial direct current stimulation – a concise review with applications to stroke

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In the past few years, there has been a rapid increase in the application of non-invasive brain stimulation to study brain-behavior relations in an effort to potentially increase the effectiveness of neuro-rehabilitation. Transcranial direct current stimulation (tDCS), an emerging technique of non-invasive brain stimulation, has shown to produce beneficial neural effects in consequence with improvements in motor behavior. tDCS has gained popularity as it is economical, simple to use, portable, and increases corticospinal excitability without producing any serious side effects. As tDCS has been increasingly investigated as an effective tool for various disorders, numerous improvements, and developments have been proposed with respect to this technique. tDCS has been widely used to identify the functional relevance of particular brain regions in motor skill learning and also to facilitate activity in specific cortical areas involved in motor learning, in turn improving motor function. Understanding the interaction between tDCS and motor learning can lead to important implications for developing various rehabilitation approaches. This paper provides a concise overview of tDCS as a neuromodulatory technique and its interaction with motor learning. The paper further briefly goes through the application of this priming technique in the stroke population.

Keywords: tDCS, motor learning, TMS, corticospinal excitability, motor cortex, cortical priming, non-invasive brain stimulation

INTRODUCTION

Non-invasive brain stimulation involves modulation of the central nervous system by electrically activating neurons in the brain (Dymond et al., 1975). The past decade has seen a rapid increase in the application of non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). These neuromodulatory techniques have been widely studied in an effort to provide support for their use as therapeutic adjuvants to enhance functional recovery after impairment. Because of its relative ease of use, portability, and decreased safety risk compared to other neurostimulatory protocols, tDCS is emerging as an effective and versatile clinical tool to prime the neuromotor system prior to or during rehabilitation. As "functional improvement after injury is a relearning process" (Kleim and Jones, 2008), in this review we will provide a brief overview on the application of tDCS to enhance motor skill learning in healthy humans and the physiological mechanisms associated with it. We will also briefly review articles that have used tDCS to enhance motor performance in stroke survivors. Understanding the interaction between tDCS and motor learning can lead to important implications for optimizing neuro-rehabilitation.

REVIEW CRITERIA

A search of the literature through January 2012 was performed in the following databases: PubMed, Web of Science, and OVID. The keywords "tDCS and motor learning," "tDCS and motor performance," and "tDCS and stroke" were used. Peer reviewed studies were selected if they met the following inclusion criteria: (1) written in English, (2) involved more than one human participant, and (3) included MEP amplitude and/or at least one motor performance-based outcome measure. Because of the vast number of studies that have used tDCS and the presence of numerous review articles on tDCS, we focused on articles relevant to the context of this paper. Data on participants, study design, analysis, follow-up, and outcomes were abstracted. Only studies rated as good or fair by the first author were included. Results were then summarized for the review.

PARAMETERS OF tDCS

Transcranial direct current stimulation involves delivering a low intensity direct current between two sponge electrodes, which are typically moistened with NaCl solution and placed on the scalp (Priori et al., 1998; Nitsche and Paulus, 2000). NaCl solution is usually preferred as it minimizes discomfort (Dundas et al., 2007). The active electrode (size between 5 and 35 cm^2) is conventionally placed on the area of the brain to be stimulated. The other electrode (usually equal or larger size than the active electrode) is placed on a region contralateral to this placement; such as the forehead if the stimulated area is the primary motor cortex. Typically current intensities of 0.5–2 mA are applied for a duration of 5–20 min, yielding a current density of 0.02–1 mA/cm^2, and a total charge between 15 and 100 $\mu C/cm^2$.

The efficacy of tDCS depends on current density which determines the induced electrical field strength (Parazzini et al., 2011). Depending on electrode dimensions, position, and the current density, approximately half of the current injected during tDCS is shunted through the scalp (Miranda et al., 2006; Sadleir et al., 2010). Low intensity currents when applied for even short periods of 10–13 min have shown to induce cortical excitability changes lasting up to 90 min (Nitsche and Paulus, 2000, 2001). These changes in corticospinal excitability, as measured by TMS evoked motor potentials, range from 40 to 150% above baseline values for anodal stimulation, and 20 to 50% below baseline values for cathodal stimulation (Nitsche and Paulus, 2000, 2001). In order to induce after effects, Nitsche and Paulus (2000) showed that a stimulus duration of at least 3 min at 1 mA or an intensity of 0.6 mA for 5 min is required. Anodal stimulation typical enhances cortical excitability while cathodal stimulation decreases excitability (Nitsche and Paulus, 2001; Nitsche et al., 2003b). These effects have been more robust in the upper limb representations compared to the lower limb motor representations.

SAFETY AND ADVERSE EFFECTS OF tDCS

Because tDCS does not involve direct brain-electrode interface and uses low currents, it can be used safely without adverse risks. The density and charge values that are conventionally used compare well with two safety studies that reported no neural damage or change in cognitive function with applied current charges less than 96 $\mu C/cm^2$ (Nitsche and Paulus, 2001; Iyer et al., 2005). However special care should be taken if the patient has alteration of the skull, such as trepanation or fracture, or if the patient has decreased integrity to the skin surface, as it may result in tissue damage because of increased current densities.

During current application, neurally driven vasodilatation may result in transient mild redness below the electrode surface (Durand et al., 2002). A study by Poreisz et al. (2007), focusing on the safety aspects of tDCS, reported a mild tingling sensation as the most common adverse effect; observed by 71% of the subjects during and 8% after the stimulation. Moderate fatigue was the second frequent adverse effect and a light itching sensation under the electrodes occurred in 30% of the subjects during the stimulation and in 15% after the stimulation. Very few subjects felt a slight burning sensation or a mild pain sensation under the electrodes. About 11% reported difficulties in concentrating during tDCS whereas headache seemed to occur in 5% of cases during and 12% after stimulation.

Care should be taken that there are no metallic implants near the electrodes. None of the tDCS studies have reported any serious complications of stimulation, such as seizure or instance of psychotic symptoms. However, it is necessary to keep in mind that anodal tDCS increases cortical excitability and it may be prudent to exclude patients at risk for epileptic seizures. In addition, repetitive application and long durations of tDCS should be carefully monitored for adverse effects even though none have been reported so far. Thus, to the best of our knowledge, tDCS protocols that have been conventionally used appear to be safe and the side effects are commonly limited to focal tingling, itching, and a local erythema, making it a preferred technique of choice.

MECHANISM OF ACTION

DURING STIMULATION

During stimulation, effects of tDCS are primarily based on the principle of modulation of neuronal membrane potential, altering the conductance of sodium and calcium channels. Depending on the polarity of stimulation (anodal vs. cathodal), tDCS induces spontaneous neuronal excitability by a tonic depolarization or hyperpolarization of the resting membrane potential (Creutzfeldt et al., 1962; Purpura and McMurtry, 1965). Anodal (positive) stimulation increases the spontaneous firing rate and the excitability of cortical neurons by depolarizing the membranes, while cathodal (negative) stimulation leads to hyperpolarization of the neuronal membranes resulting in decreased neuronal firing rate and excitability. In addition to polarity changes in the superficial membranes, Creutzfeldt et al. (1962) demonstrated that neurons in the deeper layers of the cat motor cortex are stimulated by cathodal and inhibited by anodal stimulation, probably as a result of the inversion of current flow associated with the neuron's spatial orientation. Hence it is important to keep in mind that tDCS could create dissimilar levels of polarity in the deeper layers.

POST-STIMULATION

The after effects of tDCS are not simply because of prolonged membrane potential shifts, but also due to mechanisms similar to long-term potentiation (LTP) and long-term depression (LTD) (Islam et al., 1995; Nitsche and Paulus, 2000; Nitsche et al., 2003a). NMDA-receptor modulation is involved in the induction of LTP- and LTD-like mechanisms. Activation of the NMDA receptors results in an increase in intracellular calcium in the post synaptic neuron. A small increase in the post synaptic calcium levels leads to LTD- and a greater increase induces LTP-like mechanisms (Lisman, 2001). After effects of tDCS are presumably driven by the activation of the NMDA receptors. Dextromethorphan (DMO), a NMDA-receptor antagonist has been reported to suppress the post-stimulation effects of both anodal and cathodal stimulation (Liebetanz et al., 2002; Nitsche et al., 2003a). NMDA-receptor efficacy depends on intracellular calcium level (a prolonged calcium increase enhances NMDA-receptor efficacy, while a low calcium level reduces it; Bennett, 2000; Lisman, 2001). By applying calcium channel blockers during stimulation, Nitsche et al. (2003a) showed that tDCS elicits modifications in NMDA receptors via changes in intracellular calcium concentration.

Evidence also suggests the involvement of inhibitory GABAergic synapses for the after effects of tDCS. Using a paired pulse TMS protocol to measure intracortical inhibition, Nitsche et al. (2005) reported a prominent involvement of intracortical inhibitory mechanisms for the resulting excitability modulations. Anodal tDCS resulted in a reduction of short latency intracortical inhibition and an increase in indirect wave (I-wave) facilitation, suggesting a decrease in the GABA interneuronal activity. Stagg et al. (2009) further demonstrated that 10 min of anodal tDCS significantly decreases GABA concentration. The after effects of cathodal tDCS are also dependent on modulation of GABAergic and in addition glutamatergic synapses. In the above mentioned paired pulse TMS study by Nitsche et al. (2005), cathodal stimulation led to a significant decrease in intracortical facilitation. Stagg et al. (2009) reported that the concentration of glutamate

was significantly decreased within the cathodally stimulated cortex. In addition to NMDA, GABA, and glutamate involvement, the after effects of tDCS are also modulated by serotonin, dopamine, and acetylcholine (Kuo et al., 2007, 2008; Nitsche et al., 2009a,b). More recently, tDCS has also been reported to enhance brain derived neurotrophic factor (BDNF) secretion and tyrosine receptor kinase B (TrkB) activation which are also critical factors for augmentation of synaptic plasticity and motor learning (Fritsch et al., 2010).

Although the mechanisms of action of tDCS are not yet completely understood, we can conclude that tDCS not only alters spontaneous neuronal firing rate by altering the resting membrane potential, but it helps to produce neuroplastic changes by altering synaptic function.

TRANSCRANIAL DIRECT CURRENT STIMULATION AND MOTOR SKILL LEARNING IN INDIVIDUALS WITHOUT NEUROLOGICAL DISORDERS

Motor skill learning refers to the process by which movements are executed more quickly, accurately, and efficiently with practice (Willingham, 1998). Technological and methodological advances in neuroimaging as well as non-invasive brain stimulation have provided us with a greater understanding of the neural substrates involved in skill acquisition. Motor skill learning is typically characterized by increased functional connectivity in a distributed network that involves the primary motor (M1), premotor, and supplementary motor cortices, the cerebellum, thalamic nuclei, and the striatum (Honda et al., 1998; Ungerleider et al., 2002; Seidler, 2010). At the neural level, motor skill learning is accompanied by changes in neuronal activity and excitability, and synaptic plasticity (Dayan and Cohen, 2011). Mechanisms like LTP and LTD are widely considered major cellular mechanisms underlying learning and memory (Bliss and Collingridge, 1993; Rioult-Pedotti et al., 2000).

The physiological basis of tDCS, as described earlier, is analogous to the mechanisms that accompany motor learning. As the M1 is involved critically in motor skill learning (Shmuelof and Krakauer, 2011), many studies have targeted the M1 to facilitate motor learning processes using tDCS, either by enhancing excitability in the learning M1 using anodal stimulation or by decreasing excitability in the resting M1 via cathodal stimulation. In the following section we present animal and human studies that have applied tDCS to the healthy brain to augment motor skill learning.

tDCS OF THE UPPER LIMB MOTOR CORTEX

Early studies on primates have associated anodal tDCS of the cortical surface with improved learning (Rosen and Stamm, 1972). Almost two decades later, Nitsche et al. (2003c) studied the effects of tDCS on implicit motor learning in humans by exploring hand motor performance during a variant of the serial reaction time task. tDCS was applied separately to the M1, premotor, and prefrontal cortices during performance of the motor task. It was found that the reaction time of the skilled task decreased during facilitatory anodal tDCS stimulation compared to inhibitory cathodal or sham stimulation. This improvement was primarily noted during stimulation of the M1 and not the other areas. These results have also been supported by many other studies, which have shown that increasing excitability of the learning M1 using anodal stimulation leads to improvements in motor learning (Jaeger et al., 1987; Boggio et al., 2006). More recently, Stagg et al. (2011) examined the effects of tDCS over the M1 during an explicit motor learning task consisting of sequential finger presses. Similar to previous motor learning studies on implicit behavior, they showed that application of tDCS during motor practice led to modulation of behavior in a polarity specific manner as compared to sham in which anodal tDCS led to faster learning and cathodal tDCS slowed down learning. In this study tDCS was found to modulate both the total amount of learning as well as the rate of learning.

Reis et al. (2009) examined repeated applications of anodal tDCS on M1 during motor skill learning over five consecutive days. A skill measure that reflected shifts in the task's speed–accuracy tradeoff was chosen. Anodal tDCS not only led to significant greater total learning but the enhanced skill measure remained superior in the anodal group compared to sham tDCS even at 3 months, suggesting that tDCS not only enhances motor learning but can also positively influences long-term consolidation. In addition to enhancing motor learning, de Xivry et al. (2011) demonstrated that anodal tDCS of the M1 also has the capacity to enhance generalization of learning. In this study, healthy participants adapted to a force field by reaching to a single target in one trained direction and were later tested for generalization in another workspace. Interestingly stimulation of the M1 (and not the adjacent posterior parietal cortex) enhanced the generalization process in the intrinsic coordinates of the joints and muscles but did not affect the extrinsic coordinates (environment), a finding highly relevant to rehabilitation.

Anodal tDCS over the M1 during motor practice has also been shown to enhance coding and retention of motor memory (Galea and Celnik, 2009). However, when anodal TDCS is applied during the last phase of motor training, it is shown to have a negative effect on motor memory formation (Rosenkranz et al., 2000). Similar studies using repetitive TMS have shown that the same TMS protocol can be facilitatory or inhibitory depending on the prior state of the system (Siebner et al., 2004; Iezzi et al., 2008; Kantak et al., 2010). Hence it is possible that the effects of tDCS also depend on the prior state of the corticomotor system.

Fritsch et al. (2010) examined molecular mechanisms underlying the effect of tDCS on motor skill learning using a mouse model. This group showed that tDCS is beneficial to motor learning when BDNF release occurs through training and that in the absence of activity-dependent BDNF secretion (conditional BDNF knockout mice), the beneficial effects of tDCS may not materialize. They further reported that anodal tDCS with combined repetitive low-frequency synaptic activation induces LTP that is NMDA-receptor dependent and mediated by secretion of BDNF.

tDCS OF THE VISUAL CORTEX

In addition to its effects on the M1, tDCS has also shown to have effects on the extrastriate visual area (V5) known to mediate motion processing and contribute to visuo-motor learning. Antal et al. (2004) tested visuo-motor learning by enhancing the excitability of the M1, the primary visual cortex, and the extra

striate visual area (V5) using anodal tDCS with three different electrode configurations in different groups of subjects. Facilitatory stimulation of the M1 and V5 resulted in improved performance during the early learning phase of the visually guided manual tracking task. Cathodal stimulation did not show any effect. As visuo-motor tasks highly depend on visual perception and cognitive processing, tDCS could possibly modulate either of these processes contributing to motor learning.

tDCS OF THE DORSOLATERAL PREFRONTAL CORTEX

Memory enhancement is of interest to those involved in rehabilitation as behavioral changes during learning are implemented by memory processes in the brain (Maxwell et al., 2003; Kantak and Winstein, 2012). There is evidence that anodal tDCS of the dorsolateral prefrontal cortex (DLPFC) enhances working memory. Working memory refers to temporary storage of information to be made available for future information processing. Working memory is also crucial to many higher-order strategic functions and plays a central role in long-term memory. The DLPFC plays a crucial role during working memory tasks (Butefisch et al., 2004). Fregni et al. (2005) investigated the effects of anodal stimulation of the DLPFC on working memory. Subjects performed a three-back working memory tasks based on letters during tDCS application over the DLPFC. Although there was no significant difference with respect to the response time, results showed increased correct responses and less errors with anodal stimulation of DLPFC compared to cathodal or sham of the DLPFC, or anodal stimulation of the M1. Zaehle et al. (2011) added further evidence to the interaction between tDCS and working memory by investigating the modulatory effects of tDCS on the underlying oscillatory brain activity with electroencephalography (EEG). At the level of neural ensemble, synchronized activity of a large number of neurons gives rise to oscillations that can be observed using EEG. Using a two-back letter memory task, the authors found a significant effect of stimulation in which the participants responded faster and showed improved performance after anodal tDCS compared to sham and cathodal tDCS. An increase in oscillatory power after anodal tDCS and a decrease in oscillatory power after cathodal tDCS was observed. Changes in oscillatory brain activity play an important role in the formation of perception and memory and thus are essential for higher cognitive functions. This study highlights the potential application of tDCS in pathologies that have not only been associated with memory deficits but also involve alterations of oscillatory brain activity.

tDCS OF THE CEREBELLUM

A few recent studies have targeted the cerebellum for the application of tDCS as it is a critical structure involved in movement control and cognitive processing. Galea et al. (2009) showed that tDCS is capable of modifying cerebellar excitability. Cathodal tDCS decreased and anodal tDCS increased cerebellar inhibition of M1. This change in excitability lasted for 30 min after stimulation and did not affect the excitability of the brainstem or corticomotor system. Anodal cerebellar tDCS also helped subjects adapt faster to a novel visuo-motor transformation paradigm compared to M1 stimulation. However, tDCS of the M1 resulted in a marked increase in retention of the task (Galea et al., 2011).

tDCS OF LOWER LIMB AREAS

All of the studies mentioned above are related to upper limb motor tasks. Studies examining the effects of tDCS on lower limb motor learning are limited. Because of the proximity of the two lower limb motor cortices, targeting tDCS to one hemisphere without inducing a same sign modulation in the opposite hemisphere is a challenge. Using a combination of carefully selected electrode size and position, Madhavan and Stinear (2010) successfully applied tDCS to one lower limb M1 while creating an opposite sign modulation in the other M1. They also noted that it was possible to focally up regulate one hemisphere in almost 80% of subjects tested. Although anodal tDCS has shown to successfully enhance cortical excitability of the lower limb muscle representations, cathodal tDCS does not reveal the expected downregulation of excitability that is commonly reported in upper limb studies (Jeffery et al., 2007).

Tanaka et al. (2009) applied anodal tDCS to the lower limb M1 and showed that the facilitatory tDCS can improve maximal leg pinch force and that this improvement is retained for approximately 30 min after the end of stimulation. This effect was specific only to leg motor performance and did not influence hand function suggesting spatial specificity of the effects of tDCS. Recently, Jayaram et al. (2012) showed that cerebellar tDCS can increase or decrease the rate of adaptation to a novel task depending on anodal or cathodal tDCS (respectively) over the cerebellum during a specific cerebellar-dependant locomotor training paradigm.

To summarize, tDCS applications in the healthy brain open up the possibilities of using tDCS as an experimental and rehabilitation tool for understanding and improving upper extremity and lower extremity motor function and learning.

USE OF tDCS FOR FUNCTIONAL RECOVERY IN STROKE

Relearning of motor skills is a fundamental process for recovering motor function after neurological injury such as stroke (Carr and Shepherd, 1987; Kleim and Jones, 2008). Learning is required for both recovery (restoring the ability to perform movement in the same manner as it was performed prior to injury) and compensation (performing a task in a manner different from how it was performed prior to injury (Krakauer, 2006; Kleim, 2011)). Since it is still debated whether individuals with stroke have true motor learning deficits, and whether recovery from stroke is indeed a form of model-free motor learning (Krakauer, 2006), in this paper we choose to focus on the application of tDCS in stroke in the context of training-induced improvements in motor function as most papers cited below have tested only changes in motor function in stroke patients after single or repeated applications of tDCS.

The use of tDCS in stroke is based on the model of interhemispheric imbalance. In healthy individuals, balance between-hemisphere corticospinal excitability is maintained via transcallosal inhibitory connections, whereby each hemisphere acts to inhibit the other. Typically after stroke, the non-lesioned M1 becomes hyperexcitable because of decreased transcallosal inhibition imposed by the lesioned hemisphere (Traversa et al., 1998). Primarily this imbalance in between-hemisphere corticospinal excitability is suggested to be maladaptive and a marker of poor

functional recovery (Rossini et al., 2003; Ward et al., 2003; Serrien et al., 2004; Duque et al., 2007; Madhavan and Stinear, 2010). Further evidence for this can be found in training studies where post-training improvement in upper limb and lower limb motor function is associated with a decrease in the excitability of the non-lesioned M1 or increase in the excitability of the lesioned M1 (Muellbacher et al., 2002; Lin et al., 2008; Yen et al., 2008). Consistent with this idea, many have used tDCS to manipulate cortical excitability to facilitate motor learning and enhance the effects of traditional therapy. Up regulating the lesioned hemisphere with excitatory stimulation or down regulating the non-lesioned M1 with inhibitory stimulation may help redress the symmetry in between-hemisphere corticomotor excitability and enhance motor learning. Cortical stimulation, in combination with a suitable motor therapy, may be a new treatment option to increase the effectiveness of rehabilitation (Krakauer et al., 2012). The idea behind this approach is that combined peripheral activities and central brain stimulation can enhance synaptic plasticity and motor skill acquisition by modulating the afferent inputs to the cortex when it is centrally stimulated.

UPPER LIMB

Numerous studies have reported the beneficial effects of anodal tDCS on the lesioned M1 or cathodal tDCS over the non-lesioned M1 in improving motor performance of the affected limb in patients after stroke. Details of these studies are characterized in **Table 1**. Ten to fifteen minutes of tDCS before or during performance of skilled movement tasks has resulted in approximately 10–20% improvement in paretic upper limb motor function after single or multiple sessions of tDCS. In some studies (particularly those with repeated stimulation), the effects have outlasted stimulation from 24 h up to 6 months (Boggio et al., 2007; Hesse et al., 2007; Kim et al., 2010; Bolognini et al., 2011; Nair et al., 2011; Zimerman et al., 2012). Most of these studies have used upper limb motor performance measures such as Jebsen Taylor Hand Function Test and Upper Extremity Fugl-Meyer Scale. Although these studies provide valuable data regarding changes in clinical function, not much information on the neural or motor mechanisms that resulted in these improvements is reported. It should also be noted that the magnitude of improvement is varied among studies and may be dependent on the dosage of tDCS delivered, the type of patients recruited (acute, sub-acute, or chronic), outcome measure used and the type of task performed in conjunction with tDCS. As in many stroke studies, not all subjects have shown the expected improvement.

LOWER LIMB

There is relatively less evidence for the effects of tDCS on lower limb motor function post stroke. Madhavan et al. (2011) were the first to report purposeful modulation of ankle motor practice in stroke patients after facilitatory stimulation of the lesioned lower limb M1. This improvement with motor practice seen with anodal stimulation was not observed with sham stimulation or anodal stimulation of the non-lesioned lower limb M1, emphasizing the polarity specific and focal effects of tDCS. Similarly, Tanaka et al. (2011) showed that a single session of facilitatory tDCS is capable of enhancing quadriceps extensor force in chronic patients. Despite the promising preliminary effects of tDCS on lower limb motor control and strength, in contrast Geroin et al. (2011) found that applying anodal tDCS in combination with robotic gait training did not enhance the effects of robotic gait training in stroke patients. Whether a different dosage of stimulation or combining tDCS with a different gait training paradigm will be beneficial to enhance outcomes of gait training is yet to be determined.

Bi-HEMISPHERIC STIMULATION

Studies are also now beginning to examine the effects of bi-hemispheric brain stimulation using tDCS. Lindenberg et al. (2010) investigated whether tDCS modulation of bilateral motor cortices in combination with physical and occupational therapy improves motor outcome after stroke. They used anodal tDCS to upregulate excitability of lesioned M1 and cathodal tDCS to downregulate excitability of the non-lesioned M1. A significant improvement (∼20%) in motor function scores was seen with simultaneous bilateral modulation. The effects outlasted the stimulation by at least 1 week. The authors suggested that cathodal stimulation helps augment the direct effects of the anodal stimulation through additional modulation of inter-hemispheric interactions.

In summary, tDCS has revealed preliminary success in enhancing motor learning and recovery in stroke patients. tDCS has a greater advantage over other non-invasive brain stimulation techniques in a clinical setting because of its low-cost (approximately $500 per device), ease of use, portability, and low risk. However, individualized options with tDCS need to be investigated in patients especially regarding dosage of current, site of stimulation, time of window of stimulation, and type of therapy to perform in conjunction with stimulation. It is also important to consider the residual anatomical and physiological substrates available to each patient before prescribing tDCS. Upregulating the lesioned M1 or down regulating the non-lesioned M1 may not necessarily be the optimal approach for all patients. For example: if a patient's anatomical resources in the lesioned hemisphere are limited, then suppressing the non-lesioned M1 may be of concern and upregulation of the non-lesioned M1 could be an option. This is a hypothesis that needs to be tested.

LIMITATIONS

Although most of the studies presented above depict an optimal picture of desired modulation of cortical excitability in conjunction with improvements in motor performance and motor learning, it is necessary to remember that tDCS research is still in its preliminary stage and has several associated caveats: (1) Most previous investigations have focused on short-term improvements in performance and learning. Larger experimental and clinical trials are required to assess the effects of repeated applications of tDCS in association with multiple training sessions, their interaction with specific motor learning stages and tasks, and the extent to which these performance improvements cause clinical changes and aspects of safety. (2) For the successful implementation of this technique as an interventional strategy, a better understanding of the underlying neurophysiological mechanisms is essential.

Table 1 | Summary of study characteristics.

Studies included	Sample population	Study design	Type of tDCS	Number of sessions	Time of testing	Outcome measure	Change in performance
Zimerman et al. (2012)	Chronic Stroke	Double blind, crossover, sham controlled	Cathodal during training	Single	During, 90 min and 24 h after the intervention	Performance of a complex sequential finger movement task of paretic hand	Improvement
Rossi et al. (2012)	Acute Stroke	Double blind, sham controlled	Anodal during rest	Repeated (5 daily sessions)	Onset, at 5 days and after 3 months	(1) Short form of Fugl-Meyer motor scale; (2) National Institute of Health Stroke Scale; (3) Barthel Index; (4) Modified Rankin Scale	No difference
Nair et al. (2011)	Chronic stroke	Double blind, sham controlled	Cathodal combined with OT for paretic arm and hand	Repeated (5 daily sessions)	(1) ROM: baseline, after 5 days and again 7 days later; (2) upper Extremity – Fugl-Meyer: baseline and 7 days after intervention	(1) ROM for upper extremity; (2) Upper Extremity Fugl-Meyer	Improvement
Bolognini et al. (2011)	Chronic Stroke	Double blind, sham controlled	Bi-hemispheric followed by CIMT for paretic hand	Repeated (10 daily sessions)	Baseline, day 1, day 5, day 10 (end of treatment) and at 2 and 4 weeks follow-up	(1) Jebson Taylor Test; (2) Hand grip strength; (3) Motor Activity Log Scale; (4) Fugl-Meyer Motor scale	Improvement
Tanaka et al. (2011)	Chronic Stroke	Double blind, crossover, sham controlled	Anodal during paretic quadriceps contraction	Single	Before, during, and 30 min after tDCS	Maximal knee-extension force measured with handheld dynamometer	Improvement
Madhavan et al. (2011)	Chronic Stroke	Single blind, crossover, sham controlled	Anodal during paretic ankle target tracking	Single	Before, during, and after	Tracking accuracy	Improvement
Geroin et al. (2011)	Chronic Stroke	Pilot randomized clinical trial	Anodal combined with robot assisted gait training	Repeated (10 sessions over 2 weeks)	Baseline, immediately after and 2 weeks post treatment	(1) Six-minute walking test (2) 10-m walking test	No difference
Lindenberg et al. (2010)	Chronic Stroke	Sham controlled	Bi-hemispheric combined with PT/OT of paretic upper limb	Repeated (5 daily sessions)	Baseline, after 3 and 7 days post intervention	(1) Upper Extremity Fugl-Meyer; (2) Wolf Motor Function Test	Improvement
Kim et al. (2010)	Sub-acute Stroke	Single blinded, sham controlled	Anodal, cathodal, or sham combined with OT of paretic upper limb	Repeated (10 days sessions)	Baseline, 1 day after and 6 months after	(1) Upper Extremity Fugl-Meyer; (2) Barthel Index	Improvement

(Continued)

Table 1 | Continued

Studies included	Sample population	Study design	Type of tDCS	Number of sessions	Time of testing	Outcome measure	Change in performance
Boggio et al. (2007)	Chronic Stroke	Exp 1: double blind, cross over, sham controlled,	Exp 1: anodal, cathodal, and sham at rest Exp 2	Exp 1: repeated (4 weekly sessions) Exp 2: 5	Exp 1: baseline, following session 1 and session 4. Exp 2: baseline	Jebson Taylor Test	Improvement
		Exp 2: open label study	Cathodal at rest	Consecutive daily sessions	During and 1 and 2 weeks after intervention		
Hesse et al. (2007)	Sub-acute Stroke	Pre-post	Anodal tDCS with robot assisted arm training of paretic limb	Repeated (30 sessions over 6 weeks)	Pre–post	(1) Upper extremity Fugl-Meyer; (2) Aachener Aphasia Test	Mixed results (only 3/10 improved)
Hummel et al. (2005)	Chronic Stroke	Double blind, crossover, sham controlled	Anodal during Jebsen Taylor test	Single	Baseline, during, post and 10 days after intervention	Jebson Taylor Test	Improvement

ROM, range of motion; OT, occupational therapy; PT, physical therapy; CIMT, constrained induced movement therapy; tDCS, transcranial direct current stimulation.

(3) Because of inter-individual differences in conductivity, scalp resistance, and orientation of the cortical neurons, precise current flow cannot be predicted. Indeed, there is substantial variability in the after effects of tDCS. Madhavan et al. (2010) found that the same dosage of facilitatory stimulation that induced upregulation in majority of subjects downregulated cortical excitability of the lower limb motor cortex for some. Hence, some measure of cortical excitability is needed to ensure that the desired upregulation was obtained. (4) There is a need for more research regarding electrode and current parameters to hone the temporal and spatial resolution of tDCS. (5) It is yet to be clear whether the effects of tDCS are optimal during online (during task performance) vs. offline (before or after task performance) stimulation. Stagg et al. (2011) showed that the application of anodal tDCS before a sequence-learning task resulted in slower learning. The importance of such timing dependence has not yet been fully explored for tDCS. (6) Most of the studies of tDCS in stroke patients have been limited to sub-acute and chronic stages of recovery. A recent study by Rossi et al. (2012) found that repeated sessions of anodal tDCS to the lesioned motor cortex applied during rest in acute stroke patients did not accelerate function recovery. Whether this was a function of application during rest instead of motor practice or the responsivity of the time of stroke is yet to be determined.

CONCLUSION AND FUTURE DIRECTIONS

Despite the above limitations, the following can be concluded about tDCS:

- There is accumulating evidence to suggest that tDCS is effective in modulating cortical excitability in most cases. Typically, anodal tDCS increases neuronal excitability and cathodal tDCS decreases neuronal excitability. As the desired modulation may not be obtained in every individual, electrophysiological measures should be included to establish the desired sign and extent of modulation especially when using this as an adjuvant to therapy.
- Upregulation of the lesioned hemisphere and/or downregulation of the non-lesioned hemisphere appears to enhance the outcomes of rehabilitation in stroke patients. tDCS is typically applied before or in conjunction with a motor task to optimize training outcomes. Hence, it is important to consider it as an adjuvant to prime the brain and not therapy itself.
- The area of stimulation should be chosen depending on the expected outcome. For e.g., facilitatory stimulation of the M1 may help better retention of a skilled motor task while stimulation over the cerebellum may help with faster adaptation to the task (Galea et al., 2009).
- To the best of our knowledge, tDCS used within conventional parameters appears to be low risk and can be used without adverse effects in patients.

In conclusion, tDCS offers a low-cost, portable, and potentially high-impact option for enhancing skilled motor learning and neuro-rehabilitation. Larger randomized controlled trials are needed for the design and optimization of tDCS as a therapeutic tool for patients after stroke.

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Transcranial direct current stimulation and behavioral models of smoking addiction

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While few studies have applied transcranial direct current stimulation (tDCS) to smoking addiction, existing work suggests that the intervention holds promise for altering the complex system by which environmental cues interact with cravings to drive behavior. Imaging and repetitive transcranial magnetic stimulation studies suggest that increased dorsolateral prefrontal cortex (DLPFC) activation and integrity may be associated with increased resistance to smoking cues. Anodal tDCS of the DLPFC, believed to boost activation, reduces cravings in response to these cues. The finding that noninvasive stimulation modifies cue induced cravings has profound implications for understanding the processes underlying addiction and relapse. tDCS can also be applied to probe mechanisms underlying and supporting nicotine addiction, as was done in a pharmacologic study that applied nicotine, tDCS, and TMS paired associative stimulation to find that stopping nicotine after chronic use induces a reduction in plasticity, causing difficulty in breaking free from association between cues and cravings. This mini-review will place studies that apply tDCS to smokers in the context of research involving the neural substrates of nicotine addiction.

Keywords: transcranial direct current stimulation, smoking, smoking cessation, repetitive transcranial magnetic stimulation, nicotine

INTRODUCTION

The vast majority of smokers who attempt to quit relapse (CDC, 2008); thus representing an urgent problem in need of additional effective treatments and one in which non-invasive brain stimulation may fill an important niche. Although the reason for this intransigency is a puzzle to neuroscientists, one of the key processes thought to underlie the high rate of relapse is the power of environmental cues to elicit cravings to smoke (Janes et al., 2010; Versace et al., 2011). While current smoking cessation aids are mainly nicotine supplements, there also has been an interest in the impact of brain stimulation on cravings and other correlates of smoking and withdrawal.

The dorsolateral prefrontal cortex (DLPFC) has been a major target of non-invasive stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). This brain region is easily accessible to non-invasive stimulation and is believed to exert cognitive control over feelings of craving and reward related to smoking (Goldstein and Volkow, 2011). While the orbitofrontal cortex (OFC) and subcortical regions also are often implicated in smoking addiction, the locations of these structures preclude them as targets for current non-invasive stimulation techniques. Models accounting for the process by which such stimulation modifies cravings focus on controlling functions of the DLPFC itself (McBride et al., 2006; Nestor et al., 2011), as well as possible downstream effects to the subcortical regions involved in the reward system (e.g., Di Chiara, 2000; Haber et al., 2006). tDCS can also be combined with other modalities such as transcranial magnetic stimulation (TMS), functional imaging, and pharmacologic manipulation to explore these multiple, distinct, neurotransmitter systems of reward, and craving. For example, a study characterized a deficit in neuroplasticity induced by lack of nicotine in chronic smokers by applying tDCS, TMS, and pharmacologic challenge (Grundey et al., 2012). Such a deficit of plasticity could be a mechanism underlying the resilience of addiction against therapy, an aspect of smoking cessation that may be possible to address by using the ability of tDCS to modulate plasticity (Nitsche and Paulus, 2000, 2001). This mini-review will place the three, existing, published, studies that apply tDCS to smokers in the context of other studies involving the neural substrates of nicotine addiction to suggest additional future research directions.

COGNITIVE PROCESSES UNDERLYING MAINTENANCE VERSUS CESSATION OF SMOKING BEHAVIOR

In smoking research, major subjects of study are craving, drug seeking behavior and related expectations, and relapse. Modulating smoking cue reactivity has been one productive target behavior for brain stimulation (Fregni et al., 2008; Boggio et al., 2009). This approach is accomplished by studying the effect of smoking cues in smokers on self-rated cravings, as smoking cue reactivity is strongly related to smoking relapse (Versace et al., 2011). Neuroimaging studies present smoking cues as stimuli meant to elicit craving responses in smokers, allowing observation of the brain's reaction. Common cues include video and photographs of people smoking, as well as tactile prompts such as both individual cigarette and pack handling. Reactions to these stimuli are controlled for by exposure to neutral but similar stimuli, such as video or pictures of non-smoking people, handling similarly shaped non-cigarette objects such as pencils. Showing such reward cues even before the rewarding substance in consumed (Childress et al., 1999), as well as vivid cognitive images of reward (Berridge

and Robinson, 2003) have been shown to activate the brain regions implicated in mediating reward in the brain.

Whereas most studies on the effect of brain stimulation on smoking focus on response to smoking cues that provoke a craving which can then be modulated, cessation of smoking brings on a second form of craving: abstinence induced craving (Jarvik et al., 2000; Tiffany et al., 2000; Morissette et al., 2005). This feeling is associated with a depletion of nicotine, and is therefore more affected by nicotine than cue induced craving (Tiffany et al., 2000; Morissette et al., 2005). Interestingly, abstinence craving has been shown to be a more effective predictor of relapse than cue induced craving (Killen and Fortmann, 1997; Shiffman et al., 1997). Functional imaging studies show that abstinence craving is associated with activation increases in the right DLPFC and OFC as well as the thalamus (McClernon et al., 2005; Wang et al., 2007) suggesting that they play roles in maintaining abstinence as well as cue induced cravings (**Table 1**).

DLPFC: STIMULATION AND IMAGING

Several imaging studies of smokers have demonstrated that activation in the DLPFC increases in response to seeing smoking cues (**Table 1**; but, see David et al., 2005). It is generally believed that this activation reflects increased cognitive control (Goldstein and Volkow, 2011). There have been multiple thoughtful and creative paradigms used to elucidate mechanisms underlying how control processes modulate smokers' response to stimulus cues, including control of motivation, selective attention, working memory, learning, decision making/anticipation, and self-control/behavioral monitoring such as response inhibition. For example, McBride et al. (2006) showed that, even when self-rated craving was equivalent across subjects, the expectation of being able to smoke led to higher DLPFC activation. They concluded that models of control processes of DLPFC should include expectancy and a behavioral system involved in planning and drug seeking.

Because smoking is a known vascular risk (AHA et al., 2012), it is not surprising that neuroimaging studies reveal changes in the structural and functional integrity of the DLPFC that are related to measures of addiction. Long term smoking is associated with decreased gray matter volume of the DLPFC (Brody et al., 2004; Gazdzinski et al., 2005; Gallinat et al., 2006). Studies that performed multimodal imaging (Zhang et al., 2011) showed that this decrease in gray matter density in DLPFC correlated with lower activation of smoker's brains and greater lifetime exposure to cigarettes. Nestor et al. (2011) found that regardless of the cue type, smokers had less DLPFC activation than both controls and ex-smokers. Lower frontal lobe activation, specifically right superior frontal gyrus (SFG/BA10), during fMRI was associated with higher scores on a measure of nicotine dependence (Fagerström test of nicotine dependence) and more errors on a measure of cognitive control (Go/No-Go). These findings suggest that diminished frontal lobe activation is behaviorally relevant to active smokers. The fact that former smokers did not show this relationship suggests either that there was restoration of frontal lobe functioning after a period of abstinence, or alternatively that successful prefrontal cortex performance facilitated abstinence (Nestor et al., 2011). Thus, increased activation may be a predictor of favorable outcome. Given the evidence that decreased DLPFC integrity is related to smoking history and measures of cognitive dysfunction, this raises the question of whether all smokers could benefit to the same degree from non-invasive brain stimulation. Studies which show that upregulating the frontal lobe improves smoking-related symptoms suggest that even if future studies find that diminished DLPFC ultimately is associated with poorer outcome, these patients may have a greater need for non-invasive stimulation.

High frequency rTMS of the DLPFC, believed to upregulate activation with or without cues, has been shown to both reduce cravings as well as the actual numbers of cigarettes consumed (**Table 2**). This effect was nearly immediate, with patients showing a significant same day reduction in the number of cigarettes smoked with active rTMS, but not sham controls (Eichhammer et al., 2003). Rose et al. (2011) found similar results stimulating

Table 1 | Dorsolateral prefrontal cortex implication in smoking cue reactivity – studies reporting DLPFC activation in response to smoking cues.

Author (year)	Imaging technique	Cues	Side	Inc/dec	When
Brody et al. (2002)	PET	Video, cigarette handling	Bi	Inc	With increased craving
Due et al. (2002)*	fMRI	Images	L	Inc	With smoking cues
Franklin et al. (2007)	fMRI	Video, cigarette handling	L	Inc	As craving decreases
Hartwell et al. (2011)*	fMRI	Images	R	Inc	resisting urge to smoke when shown smoking cue
Kober et al. (2010)	fMRI	Images	L	Inc	As craving decreases
Lee et al. (2005)*	fMRI	Images	R	Inc	With smoking cues
McBride et al. (2006)	fMRI	Video	Bi	Inc	With smoking cues in Expectant group
McClernon et al. (2005)*	fMRI	Abstinence	Bi	Inc	With increased craving
Versace et al. (2011)	fMRI	Images	L	Inc	With increased smoking cue reactivity
Wang et al. (2007)	ASL perfusion MRI	Abstinence	R	Inc	With increased craving
Wilson et al. (2005)	fMRI	Cigarette handling	L	Inc	With smoking cues in Expectant group
Wilson et al. (2012)	fMRI	Cigarette handling	L	Inc	With smoking cues
Zhang et al. (2011)	DTI	Images	R	Inc	With smoking cues

**Reported activation in middle frontal gyrus (MFG), which several of these papers note corresponds to DLPFC in Brody et al. (2002), dec, decrease; inc, increase; Bi, bilateral; L, left; R, right; DTI, Diffusion Tensor Imaging; fMRI, functional magnetic resonance imaging; PET, positron emission tomography.*

Table 2 | Non-invasive brain stimulation, smoking, and reward – studies reporting the effects of rTMS and tDCS on smoking, related craving, and dopaminergic reward.

Author (year)	Treatment (days)	MT (%)	Stimulation type	TMS frequency	Stimulated	Side	Cues	Result
A								
Amiaz et al. (2009)	10	100	rTMS	10 Hz	DLPFC	L	Images	Reduced cue induced cravings and consumption
Eichhammer et al. (2003)	4 (2 Sham)	90	rTMS	20 Hz	DLPFC	L	None	Reduced cigarette consumption
Johann et al. (2003)	2	90	rTMS	High	DLPFC		None	Reduced craving
Rose et al. (2011)	3	90	rTMS	10 Hz	SFG	L	View lit cigarette while handling cigarette and lighter	Increased cue induced craving, reduced general craving
						L	Cigarette smoke	Reduced craving
Soo Cho and Strafella (2009)*	1	100	rTMS	10 Hz	DLPFC	L	None	DA release in ipsilateral ACC and mOFC
						R	None	None
Strafella et al. (2001)*	1		rTMS	10 Hz	DLPFC	L	None	DA release in ipsilateral caudate nucleus
Strafella et al. (2003)*	1	90	rTMS	10 Hz	M1	L	None	DA release in ipsilateral caudate nucleus
B								
Boggio et al. (2009)	5		tDCS		DLPFC	L – anodal R – cathodal (reference)	Video, cigarette handling	Decreased cue induced craving
Fregni et al. (2008)	1		tDCS		DLPFC	L – anodal R – cathodal (reference)	Video, cigarette handling	Decreased cue induced craving
						R – anodal L – cathodal (reference)	Video, cigarette handling	Decreased cue induced craving
Grundey et al. (2012)	1		tDCS		ADM (orbit as reference)	ADM – anodal Orbit – cathodal	Abstinence	Control: no significant increase, with nicotine: increased excitability
						Orbit – anodal ADM – cathodal	Abstinence	Control: reduced excitability, with nicotine: effects abolished

*(A) Studies reporting the effects of rTMS on smoking or related craving, or the effects on dopamine release, *, not studied in smokers; L, left; R, right; ACC, anterior cingulate cortex; DA, dopamine; M1, motor cortex; MT, motor threshold; mOFC, medial orbitofrontal cortex; SFC, superior frontal gyrus. (B) Studies of the effects of tDCS on smokers; ADM, motor cortex representational area of the abductor digiti minimi muscle.*

the SFG. The longest-term study, performed by Amiaz et al. (2009) involved 10 days of rTMS treatment to the left DLPFC, followed by an additional month of maintenance. The results showed effects persisting after 6 months, a promising sign for lasting smoking cessation aid.

The success of these rTMS studies served as a basis for targeting DLPFC with tDCS (**Table 2**). Thus far there have been two studies that apply tDCS to modulate frontal lobe activity in smokers, and they have yielded promising results. In the study by Fregni et al. (2008) subjects were given randomized active or sham tDCS in conjunction with video and cigarette handling. A single anodal tDCS session over either left or right DLPFC (with cathodal stimulation on contralateral DLPFC) significantly reduced the self-reported craving levels elicited by these cues, with no significant mood changes. Furthermore, these effects were dose dependent, such that repeated sessions led to an increasingly powerful response (Boggio et al., 2009). In fact, by the end of Boggio et al.'s 5 day stimulation course, the group receiving active tDCS not only showed reduced craving ratings, but were also observed to smoke at least 30% fewer cigarettes per day, demonstrating a clinically significant effect on smoking cessation.

tDCS AS A MEASURE OF NICOTINE EFFECTS ON PLASTICITY

One process underlying nicotine addiction may involve diminished neuroplasticity induced by an absence of nicotine after chronic use. This diminished plasticity during the withdrawal state

may be an important barrier to smoking cessation, as it limits the ability of the brain to decouple the pairing between environmental cues and cravings. Nicotine influences many systems known to be involved in generating and modulating plasticity. In addition to the dopaminergic system, it affects the nicotinic acetylcholine receptors (nAChRs), as well as the adrenergic, serotonergic, glutamatergic, and GABAergic systems (Levin et al., 2006).

Because tDCS has been shown to modulate plasticity (Nitsche and Paulus, 2000, 2001), Grundey et al. (2012) applied stimulation to study the deficit of neuroplasticity associated with withdrawal. They combined paired associative stimulation (PAS), paired pulse TMS paradigm that modulates plasticity, with tDCS which can amplify these effects, to study the effect of nicotine on plasticity in smokers. In a PAS paradigm, peripheral nerve stimulation (right ulnar nerve at the wrist level) was followed by a single-pulse of low frequency TMS to the motor cortex. Depending on the interpulse interval between the two types of stimulation, the excitability of the motor evoked potential (MEP, the size of the TMS induced muscle contraction) increased (facilitation with 25 ms interpulse interval) or decreased (excitability diminishing with 10 ms interpulse interval) with repeated pairings (Stefan et al., 2000; Wolters et al., 2003). Under conditions of normal plasticity, tDCS should augment the effects of PAS with anodal tDCS increasing PAS facilitation and the cathodal tDCS reducing further the PAS excitability diminution. For smokers in withdrawal (10 h of abstinence), anodal tDCS to the motor cortex representational area of the right abductor digiti minimi muscle (ADM), using the area above the right orbit as a reference, did not significantly augment PAS facilitation, but with the addition of nicotine, there was normalization of the system such that anodal stimulation yielded a significant enhancement of excitability for hours after the stimulation was administered. Conversely, in the withdrawal condition, cathodal tDCS produced a significant decrease in excitability that was nearly abolished with the administration of nicotine. This suggests that for abstinent smokers, nicotine compensates for a deficit in plasticity which can be studied with tDCS.

FUTURE DIRECTIONS AND UNANSWERED QUESTIONS

Whereas DLPFC stimulation shows promise in reducing the power of smoking-related cues to elicit craving, brain imaging before and after therapy (e.g., MR connectivity, PET ligand studies of receptor changes) enables characterization of the network of connections between brain regions that may be indirectly altered. Affected regions might include areas involved in smoking cue reactivity such as the visual association cortex, dorsal striatum, anterior cingulate cortex, prefrontal cortex and insula, and likely the nucleus accumbens (Versace et al., 2011). Localized stimulation from both TMS and rTMS has been shown to have non-local effects (George et al., 1999; Kimbrell et al., 2002), but can only indirectly reach subcortical structures. Because tDCS involves current flow between the anodal and cathodal components, it is not known whether additional brain structures, such as the OFC which has connections to the amygdala and striatum – structures involved in mediating predictive reward value (O'Doherty, 2003) – could be directly reached with tDCS or whether the combination of both upregulation of one DLPFC and downregulation of the contralateral DLPFC can function synergistically as has been observed with tDCS of DLPFC in risk taking (Fecteau et al., 2007).

Combining pharmacologic antagonists with brain stimulation is a powerful approach for studying the neurochemical substrates of the treatment benefits of tDCS. For example, studies imaging the brain with PET ligands both before and after TMS support a model in which DLPFC stimulation indirectly modulates the brain's reward system. Strafella et al. (2001) applied rTMS to the DLPFC and showed dopamine release in brain regions implicated in addiction, notably the ipsilateral caudate nucleus, and medial prefrontal cortex, including pre- and sub-genual anterior cingulate cortex, and medial OFC, all areas implicated in addiction (**Table 2**; Soo Cho and Strafella, 2009). Eichhammer et al. (2003) posit that using TMS to increase DLPFC activation may mimic reward, and Fregni et al. (2008) suggest that stimulation with tDCS may have similar effects. This hypothetical mechanism is corroborated by a study done by Nitsche et al. (2006) showing that an antagonist that blocks the D2 receptors almost completely negates the excitability diminishing after-effects of cathodal tDCS, suggesting that dopamine receptor activation may control the induction of tDCS generated excitability. In addition to studying the connections involved, it is advantageous to have anatomical information regarding the locus of brain changes, as direct surgical stimulation of these regions might prove useful in patients where their addiction has life threatening consequences such as risk of stroke.

The rTMS, tDCS, and fMRI studies reviewed here suggest that increasing DLPFC activity should reduce craving; however, a stimulation study of craving modulation in abstinent smokers has yet to be performed. The work in Grundey et al.'s (2012) reveals that patients in withdrawal should be considered separately from those actively smoking due to a deficit in plasticity stemming from the removal of nicotine. Thus, the nicotine maintenance status of these individuals should be carefully tracked. Additionally, this lack of plasticity should be taken into consideration in all therapies involving smokers, as patients without nicotine supplementation may not benefit from therapies that depend on the form of memory that is probed by the paired associate stimulation paradigm. However, stimulation performed in conjunction with supplemental nicotine may reinstate plasticity, giving patients the ability to dissociate cue/craving pairings, and reducing the power of the cues to evoke relapse. Therefore, the therapeutic effects of tDCS could be augmented by pharmacologic intervention and combination therapies such as nicotine administration.

Furthermore, identification of multiple, distinct brain systems that mediate rewards and craving may elucidate the mechanisms by which DLPFC stimulation alters cue responsiveness. Models from the animal literature has shown that the reward system can be separated into two distinct processes; the dopaminergic "wanting" (seeing incentives as desirable compared with other stimuli) and the opiate and GABAergic "liking" (linked to conscious pleasure) pathways (Wyvell and Berridge, 2000; Reynolds and Berridge, 2002; Berridge and Robinson, 2003). Because nicotine has effects in both the "wanting" and "liking" systems of reward (Levin et al., 2006), it is possible that paired pulse paradigms could be used to probe these disparate neurotransmitter systems as Di Lazzaro et al. (2007) did by using to PAS in combination with GABA

type A receptor (GABAAR) modulating drugs to differentiate two GABAAR subtypes. Understanding the roles these reward systems play in addiction may be extremely valuable in the creation of more effective smoking treatments.

Finally, there are likely additional approaches for augmenting the tDCS treatment effects, such as manipulating the state in which the stimulation occurs, as studies of state dependency demonstrate effects on stimulation outcome (e.g., Silvanto et al., 2007, 2008; Silvanto and Pascual-Leone, 2008;). One of the critical problems for therapies is generalization. While treatments may reduce craving in the office, patients often relapse at home; the finding by Boggio et al. (2009) demonstrating reductions in cigarettes smoked after tDCS is thus compelling. However, unlike rTMS, tDCS is portable, and can therefore be delivered in the home. It remains to be seen whether stimulation under the influence of the patient's natural state of cues in their habitual smoking environment could enhance this benefit. Assessing stimulation induced reductions in smoking cue responsivity in the environment where much of their smoking behavior occurs may also be a more sensitive predictor of treatment response than similar evaluations in the lab, allowing the duration and dose of therapy to be appropriately adapted. Pragmatically, in treating smokers for whom daily TMS sessions in a clinic are not feasible, this in-home stimulation may also reach more patients. Additionally, used in conjunction with portable, mobile devices to measure psychophysiology (e.g., heart rate variability, digital palmar temperature) researchers and clinicians can move beyond the laboratory based cues into those found in patients' naturalistic settings. These devices promise to provide further clues about reactivity to stimuli in the patient's everyday life, monitoring physiological reactions to spousal conflict or other sources of acute stress, which have been shown to increase cigarette craving (Childs and de Wit, 2010). This possibility for *in vivo* study would be especially powerful if used in conjunction with longitudinal fMRI sessions with images from the patients' own environment to track changes in the neural substrates of behavior over the course of treatment. Thus, tDCS presents an opportunity to study and address several disparate barriers to smoking cessation *in vivo*: smoking cue induced craving, abstinence induced craving, withdrawal-induced neuroplasticity deficits, and the involvement of reward subtypes.

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Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke

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Introduction/Objectives: Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation are two powerful non-invasive neuromodulatory therapies that have the potential to alter and evaluate the integrity of the corticospinal tract. Moreover, recent evidence has shown that brain stimulation might be beneficial in stroke recovery. Therefore, investigating and investing in innovative therapies that may improve neurorehabilitative stroke recovery are next steps in research and development. **Participants/Materials and Methods:** This article presents an up-to-date systematic review of the treatment effects of rTMS and tDCS on motor function. A literary search was conducted, utilizing search terms "stroke" and "transcranial stimulation." Items were excluded if they failed to: (1) include stroke patients, (2) study motor outcomes, or (3) include rTMS/tDCS as treatments. Other exclusions included: (1) reviews, editorials, and letters, (2) animal or pediatric populations, (3) case reports or sample sizes $\leq$2 patients, and (4) primary outcomes of dysphagia, dysarthria, neglect, or swallowing. **Results:** Investigation of PubMed English Database prior to 01/01/2012 produced 695 applicable results. Studies were excluded based on the aforementioned criteria, resulting in 50 remaining studies. They included 1314 participants (1282 stroke patients and 32 healthy subjects) evaluated by motor function pre- and post-tDCS or rTMS. Heterogeneity among studies' motor assessments was high and could not be accounted for by individual comparison. Pooled effect sizes for the impact of post-treatment improvement revealed consistently demonstrable improvements after tDCS and rTMS therapeutic stimulation. Most studies provided limited follow-up for long-term effects. **Conclusion:** It is apparent from the available studies that non-invasive stimulation may enhance motor recovery and may lead to clinically meaningful functional improvements in the stroke population. Only mild to no adverse events have been reported. Though results have been positive results, the large heterogeneity across articles precludes firm conclusions.

Keywords: transcranial direct current stimulation, repetitive transcranial magnetic stimulation, stroke, motor, transcranial magnetic stimulation, noninvasive brain stimulation

INTRODUCTION

Stroke is a leading cause of disability in the United States. According to the American Heart Association, over 795,000 people experience strokes annually in the USA, with 185,000 presenting as recurrent strokes. Restitution of post-stroke motor function is frequently incomplete, with the majority of stroke patients unable to perform professional duties or activities of daily living by 6 months after their stroke. This becomes a self-fulfilling cycle of disability, as the decreased functional capacity predisposes toward deconditioning (or decreased physical activity) resulting in worsening cardiovascular disease and subsequent strokes (Hankey et al., 2002; Ivey et al., 2006).

The better understanding of plastic (or brain remodeling) changes following stroke have contributed to the development of novel targeted therapies that can modulate neuroplasticity, especially non-invasive methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

One important finding is the notion that plasticity is not always adaptive. Therefore, therapies that block any potential maladaptive plasticity may be desirable. Specifically, several studies show the influence of maladaptive plasticity in sustaining behavioral deficits in stroke. For instance, neuroimaging analyses of stroke subjects have noted critical increases in cortical excitability in the intact primary motor cortex (M1) of the unaffected hemisphere (Hummel and Cohen, 2006), and this increased cortical excitability has been noted to correspond with movements of the paretic arm in patients with motor impairment (Calautti and Baron, 2003;

Ward et al., 2003). In addition, the level of cortical excitability of the intact hemisphere directly correlates with the level of paresis in the affected extremity (Hummel and Cohen, 2006). Furthermore, post-stroke subjects exhibited changes in motor cortical excitability and abnormal levels of inter-hemispheric inhibition from the unaffected to the affected motor cortex (Hummel and Cohen, 2006). These observations have helped to develop the idea that there is maladaptive inter-hemispheric competition after stroke, which worsens hand paresis. Therefore, blocking or reducing maladaptive plasticity with neuromodulation techniques may be a desirable therapy as preliminary studies have shown. On the other hand, facilitatory stimulation may be provided to the affected hemisphere to enhance beneficial plasticity and improve motor outcomes (Hummel and Cohen, 2006).

Non-invasive procedures such as TMS and tDCS are elegant and powerful neuromodulatory techniques that create electric currents in the brain to change cortical excitability (Hummel and Cohen, 2006). TMS is a technique that induces a short electric pulse on the brain tissue via a varying magnetic field induced by the TMS coil, while tDCS reversibly polarizes brain regions through topical application of weak direct currents (Hummel and Cohen, 2006). Repetitive transcranial magnetic stimulation (rTMS) is a technique that provides continuous electric pulses on the brain in order to produce long-term changes in cortical excitability. Due to the relative focal target ability, safety profile, relative low cost, and positive preliminary results, these techniques have been extensively tested for the treatment of stroke.

In fact, recent studies have demonstrated that cortical brain stimulation achieved through invasive and non-invasive techniques improves motor function in stroke subjects. Small phase II trials have demonstrated that motor cortex stimulation with non-invasive techniques, rTMS and tDCS, can enhance motor function in stroke subjects significantly. The goal of this systematic review is to discuss the parameters of stimulation, clinical trial design characteristics, and evidence of effects from the available literature in the field. We (this research team) therefore reviewed clinical studies of rTMS and tDCS for motor recovery in stroke published in English from January 1st of 2002 to January 1st of 2012. We chose the period of 10 years in order to consider the most recent studies. We present our findings in the light of the state of the science and provide considerations and recommendations, with the aim of providing guidance for future studies.

METHODS

LITERATURE REVIEW

The first step of our systematic review was to perform a literature search utilizing the PubMed research database. Search strategy was implemented on PubMed to achieve higher standardization of results (Wong et al., 2006). In addition, we examined reference lists of the retrieved articles and consulted experts in the field. We performed a literary search utilizing the search terms "stroke" and "transcranial stimulation," prior to (but not including) 01/01/2012, which resulted in 695 articles. Individual search terms were used instead of mesh terms in order to increase the number of results retrieved. We added the search term "motor" to our search, which produced 513 articles. We further elucidated the results by performing two sub-search inclusions: (1) the first added the key search terms "repetitive"; (2) while the other added the search term "direct," resulting in 142 articles and 74 articles, respectively. We also cross-reference checked by using the terms "neurostimulation" and the acronyms "rTMS" and "tDCS" in lieu of their spelled-out counterparts. We found a total of 201 articles related to the use of repetitive transcranial current stimulation or tDCS in stroke patients to evaluate motor outcomes. We subsequently checked each article according to our inclusion criteria.

SELECTION CRITERIA

We included prospective studies that evaluated the effects of a treatment with rTMS and tDCS on the motor rehabilitation of patients with non-hyperacute strokes. We adopted the following inclusion criteria: (1) articles written in English; (2) non-invasive brain stimulation techniques (rTMS and tDCS) for the recovery of motor impairments in patients with non-hyperacute stroke; (3) use of scales to measure motor recovery; (4) studies published in a book, journal, proceeding, or indexed abstraction; (5) studies reporting the motor recovery scale before and after the treatment; (6) studies published with the 10-year period; and (7) treatments that included neuromodulation techniques as the main strategy to treat motor impairments in stroke. Items were excluded if they failed to (1) include stroke patients, (2) study motor outcomes, or (3) include rTMS/tDCS as treatments. Other exclusions included (1) reviews, editorials, or letters (2) animal or pediatric populations, (3) case reports or sample sizes $\leq$2 patients, (4) primary outcomes of dysphagia, dysarthria, neglect, or swallowing.

DATA EXTRACTION

The data were extracted by two authors (Bamidele O. Adeyemo and Debora Duarte Macea), using a structured form, and checked by another author (Marcel Simis). The following variables were extracted: (1) mean and SD of motor scales before and after treatment and at follow-up (when available) for the active and control groups; (2) demographic, clinical, and treatment characteristics (e.g., number of patients in the control and treatment groups, age, gender, baseline characteristics, region of stroke, type of stroke, post-injury duration, stroke severity, history of previous stroke, baseline motor function, and strength/spasticity); (3) intervention protocol type; (4) rTMS stimulation parameters (TMS type, target muscles, type of coil, frequency, intensity-%motor threshold, number of stimuli per train, inter-train interval, and number of trains); (5) tDCS stimulation parameters [intensity, duration, location, electrode (info and size)]; (6) concomitant treatments (therapy and medications); (7) methods of assessment; and (8) evaluation model and design. When a study did not report the SD for motor outcomes, we deduced them from other parameters, contacted the authors, or made note as to their availability.

QUANTITATIVE ANALYSIS AND STATISTICAL ANALYSIS

All of our analyses were performed utilizing STATA statistical software, version 8.0 (StataCorp, College Station, TX, USA). We initially computed the standardized mean difference and the pooled SD for each comparison. Given the heterogeneous motor outcomes, we focused the additional analysis to the statistically significant reports available in the article. We utilized Cohen's *d*

as an appraisal of the effect size, which was calculated by comparing pre and post-treatment mean changes of the treatment groups. Subsequently, we computed the pooled weighted effect size (weighted by the inverse variance of each study), utilizing random and fixed effect models. The random effect model lends relatively more weight to smaller studies and wider confidence intervals than the fixed effect model.

We also assessed publication bias utilizing the Begg-modified funnel plot. This figure plotted the standardized mean difference of each plot on a logarithmic scale against the respective standard error per study. We also applied the Egger's test to evaluate for any significant asymmetry. The Egger test helps identify publication bias as follows: in scenarios where the effects from the smaller studies differ from the effects reported in the larger studies, the regression line will fail to run through the origin. This might indicate publication bias where smaller studies with negative results are not published (Egger et al., 1997).

RESULTS

Our study includes 10-year data prior to 01/01/2012 of randomized clinical trials, assessing 1314 subjects (1282 stroke patients and 32 healthy subjects). The results of this systematic review suggest that the use of non-invasive brain stimulation interventions in patients with stroke are associated with improvements in motor outcomes both individually and when compared to placebo stimulation. The 50 studies showed a large variability in the type of assessments that were used, the study population, the etiology and characteristics of the stroke, and time of intervention.

STUDIES RETRIEVAL

Keyword searches on the PubMed database yielded 695 citations. Using our study criteria, we narrowed the list to 201 citations. Using our inclusion criteria, 50 articles met all our criteria and were analyzed in our review. Keyword searches on the PubMed database yielded 695 citations. Using our study criteria, we narrowed the list to 201 citations. Using our inclusion criteria, 50 articles met all our inclusion criteria and were analyzed in our review. References were excluded for (1) being non-English (narrowing to 201 citations) (2) editorial/s, review/s, letters, animal, pediatric, case reports, dysphagia, dysarthria, neglect, or swallowing (narrowing to 131 citations) (2) including the term repetitive but not related to rTMS (117 citations remaining) (3) use pain rather than motor outcomes (107 remaining citations) (4) employ theta burst or Hebbian montage (101 remaining citations) (4) not studying stroke subjects or having publication dates prior to 01/01/2012, totaling 50 meeting inclusion criteria.

DEMOGRAPHIC FINDINGS

Aggregation of participant data demonstrated a total of 1282 stroke patient participants (37% women) and the average per study was 26.04 participants. The average age of the participants was 58.46 (range of 18–95) years. (Note: the article, Lomarev et al. (2007) was not included in the average because it did not provide the necessary data to calculate average.) Demographic findings of these studies are summarized in **Table 1**.

The number of studies seemed to be stable over this 10 year period (with an average of 4.9 studies per year), though it appears that there was an increase in the last 2 years (2010 and 2011) with a peak of 13 studies. The methodological quality of the articles was assessed utilizing the Oxford quality scoring system (Jadad scale). Scores range from 0 to 3 and are listed in **Table 1** (Jadad et al., 1996; Olivo et al., 2008).

The average of the stroke duration (time after stroke) of the patients in the selected articles was 33.03 months. The individual values are represented in **Table 1**. Most of the articles included patients in the chronic stroke phase. There are six articles (Hesse et al., 2007, 2011; Dafotakis et al., 2008; Kim et al., 2010b; Sasaki et al., 2011; Conforto et al., 2012) that included subacute stroke phase and four articles (Liepert et al., 2007; Khedr et al., 2009, 2010; Chang et al., 2010) that were conducted in acute phase of the stroke. Other demographic characteristics are included in **Table 1**.

STROKE CHARACTERISTICS

We identified two articles that did not specify when the stimulation was applied regarding the time course of the stroke (Pomeroy et al., 2007; Nowak et al., 2008). Most of the studies administered stimulation during the chronic phase, rather than acute or subacute. One issue here is the definition of chronic stroke that is not well defined, which is discussed further below. The selected studies included ischemic stroke only (49.0%), both ischemic and hemorrhagic stroke, or did not specify the type of stroke (as summarized in **Table 1**).

The predominant location of the stroke was cortical and subcortical [28 (56.0%)]; followed by subcortical only [15 (30%)], cortical, subcortical, and brain stem [4 (8.2%)], subcortical and brain stem [2 (4.1%)], and one article (2.9%) did not specify the location. There were no articles reporting patients with bilateral lesions.

Most of the studies included a heterogeneous population either including the full spectrum of severity (mild to severe – 11 studies (22.4%) or at least two of the three categories (mild to moderate or moderate to severe). In four articles, it was not possible to classify the severity (Richards et al., 2006; Lomarev et al., 2007; Pomeroy et al., 2007; Kakuda et al., 2011b; Chang et al., 2012; Stagg et al., 2012).

ADJUVANT THERAPIES

Different types of therapies associated with the neuromodulation techniques as main intervention were used. The main therapies were Constraint Induced Movement Therapy (CIMT), robotic, and standard therapy (unspecified). They are listed in **Tables 3** and **4**.

MOTOR OUTCOMES

Different study designs and assessments employed in the evaluation of post-stroke motor function were used. The outcomes addressed the following: (1) motor function only; (2) safety and motor function; (3) motor function and fMRI data; (4) motor function and therapy; (5) motor function, fMRI, and therapy; and (6) motor function and voluntary muscle contraction. Specifically, we categorized all of the articles in **Table 2** according to the motor assessment tool used. We also indicated which results were reported to be statistically significant. The articles assessed for motor strength, dexterity, range of motion, and disability. This information is delineated in **Table 2**.

Table 1 | Baseline demographic characteristics of all selected peer-reviewed articles.

Reference	Number of subjects	Age-mean	Age-SD	Cortical/ subcortical	Hemorrhagic versus ischemic	Stroke severity (mild/mod/severe)	Females (%)	Stroke duration (months)	Oxford quality scoring system
Werhahn et al. (2003)	General: 20 stroke; 10 healthy	61.5	13.6	5 Cortical; 14 subcortical (2 in pons); 1 corticosubcortical	Ischemic	Mixed based MRC (1–4)	30% Healthy 40%	74.40	1
Takeuchi et al. (2005)	20	59	9.6	20 Subcortical	Ischemic	Mixed. Based FM (25–100)	25%	26.95	2
Mansur et al. (2005)	10 stroke; 6 healthy	53.3	X	3 Cortical and 7 subcortical	Ischemic	Mixed, hemiparesis 1 subtle/4 mild/3 moderate/1 severe/1 not specified (2 least excluded)	70%	X	1
Khedr et al. (2005)	52	52.85	rTMS group: 9.5; sham group: 8.4	Cortical 15; subcortical 26; corticosubcortical 11	Ischemic	Moderate to severe based NIHSS	31%	7.20	0
Fregni et al. (2005)	6	53.7	16.60	Cortical 1; subcortical 3; corticosubcortical 2	NA	Mild to moderate based on MRC (3.5–4.5)	67%	27.10	1
Fregni et al. (2006)	15	57.7	11.27	2 Cortical/13 subcortical	Ischemic	Mild to moderate motor deficit	27%	44.05	2
Lotze et al. (2006)	7 Stroke; 7 healthy	63.7	8.6	Subcortical	Ischemic	Severely paretic or even hemiplegic at their first day after stroke, four in their left hand and three in their right hand. Almost complete recovery of motor function	14%	33.90	0
Hummel and Cohen (2006)	11	57	16.00	Mostly subcortical	ischemic	Severe upper arm motor paresis (below MRC grade 2). Some of them remained unable to complete the Jebsen–Taylor Test	55%	41.80	2
Richards et al. (2006)	19	60.12	15.1	Cortical, subcortical, and brain stem	Ischemic and hemorrhagic	Mixed WMTF 19.17 (SD: 18.8)	8	81.60	3
Kim et al. (2006)	15	53.5	4.5	Cortical 5 and subcortical 10	3 Hemorrhagic, 12 ischemic	Mild to moderate rankin (1–3)	13%	16.70	1
Liepert et al. (2007)	12	63	11	Subcortical 12(2 pons)	NA	Mild based MRC (4)	33%	0.24	1
Lomarev et al. (2007)	7	X	X	2 Subcortical 5 corticosubcortical	I:6 × H:1	Sufficient residual motor function in the paretic arm to perform pinch test dynamometry (range 25.1–31.0 lb). Patients unable to extend at the metacarpophalangeal joints at least 10–20° were also excluded from the study	29%	X	0

(Continued)

Table 1 | Continued

Reference	Number of subjects	Age-mean	Age-SD	Cortical/ subcortical	Hemorrhagic versus ischemic	Stroke severity (mild/mod/severe)	Females (%)	Stroke duration (months)	Oxford quality scoring system
Malcolm et al. (2007)	19	67	6.8	NA/NA/mixed(11 MCA; 7 lacunar; 1 unlisted); cortico + subcortical	1 Hemorrhagic; 18 ischemic	Mixed based WMFT 15.5 ± 13.1 rTMS; 35.5 ± 33.9 sham	42%, 8	45.60	2
Hesse et al. (2007)	10	63.3	X	8 Cortical; 2 subcortical	Ischemic	Severe arm paresis	70%	X	3
Boggio et al. (2007)	9	57.4	12.9	Subcortical	NA	Mild-moderate based on MRC (3.7–4.8)	22%	40.90	1
Pomeroy et al. (2007)	27	74.8	12.71	Cortical 8; subcortical 17; corticosubcortical 2	Ischemic	Had upper limb weakness due to the stroke but able to produce at least a voluntary twitch of paretic biceps and/or triceps	67%	0.89	3
Nowak et al. (2008)	15	460,667	8.03	15 Subcortical	Ischemic	Mild based MRC (4–5)	27%	1.93	1
Takeuchi et al. (2008)	20	62.3	8.04	Subcortical	Ischemic	Mixed. based FM (33–91)	20%	29.90	2
Dafotakis et al. (2008)	12	45	9.00	Subcortical	Ischemic	Mild based MRC (4–5)	33%	1.88	0
Mally and Dinya (2008)	64	57.6	10.8	Cortical – large hemispheric lesion	46 Ischemic, 18 hemorrhagic	Severe	42%	129.60	0
Yozbatiran et al. (2009)	12	67	12.00	Cortical 1; subcortical 11	Ischemic, or hemorrhagic but not subarachnoid	(1) Arm motor FM score 15–55 out of 66. (2) moderate–severe arm motor deficits	17%	4.10	0
Ameli et al. (2009)	29	56	13.00	Cortical 13; subcortical 16	Ischemic	Mild-moderate	45%	5.50	0
Khedr et al. (2009)	36	57.9	11.00	Cortical 19 and subcortical 17	Ischemic	Mild to moderate	47%	0.57	1
Takeuchi et al. (2009)	30	59.3	12.4	Subcortical	Ischemic	Mixed based FM	27%	28.80	2
Kakuda et al. (2010b)	15	55	17	Subcortical 3 (1 pons); corticosubcortical 2	Hemorrhagic 9 × ischemic 6	Moderate to severe based FM (17–57)	33%	57.00	0
Grefkes et al. (2010)	11	46	9.3	Subcortical	Ischemic	Mild based MRC (4–5)	18%	1.91	1

(Continued)

Table 1 | Continued

Reference	Number of subjects	Age-mean	Age-SD	Cortical/ subcortical	Hemorrhagic versus ischemic	Stroke severity (mild/mod/severe)	Females (%)	Stroke duration (months)	Oxford quality scoring system
Khedr et al. (2010)	48	59.52	13.1	Cortical 13; Subcortical 35	Ischemic	Mixed based NIHSS	50%	0.22	2
Emara et al. (2010)	60	53.9	X	Cortical 22; Subcortical 38	Ischemic	Mild to moderate hand weakness	33%	4.16	1
Lindenberg et al. (2010)	20	58.75	14.07/12.9 (sham)	Corticosubcortical (medial cerebral artery)	Ischemic	Severe based FM (20–56)	20%/30% (sham)	35.40	3
Chang et al. (2010)	28	56.6	12.2	Cortical 11; subcortical 17 (6 pons, 2 medial medullar)	Ischemic	Mixed; mild to severe	39%; 11	0.45	2
Kim et al. (2010b)	18	57.8	X	Cortical 5; subcortical 9; corticosubcortical 4	Ischemic	Mixed based MRC (2–5) and FM (16–60)	5	0.85	3
Kakuda et al. (2010a)	5	66.8	X	subcortical	1 Hemorrhagic, 4 ischemic	Mild to moderate rankin (1–3)	2	36.60	0
Koganemaru et al. (2010)	9 Stroke + 9 Healthy	51.6 rTMS; 53.2 healthy	11.6 rTMS; 13.8 healthy	Subcortical (1 pons)	Ischemic 7; hemorrhage 2	Mixed based: Stroke Impairment Assessment Set (SIAS)	55%, 5 (both)	24.00	1
Kakuda et al. (2011b)	39	56.5	16.0	Not specified	H:23 (59); I: 16 (41)	NA (FM 36 average)	23%	50.30	0
Kakuda et al. (2011d)	52	57	13	Cortical and subcortical	Hemorrhagic 30 × ischemic 22	Brunnstrom Stage 3–5	14 (27%)	52.40	0
Kakuda et al. (2012)	204	58.5	13.4	Cortical and subcortical	hemorrhagic 107 × ischemic 97	Brunnstrom Stage 3–5	73 (36%)	60.00	0
Sasaki et al. (2011)	29	66.96		supratentorial subcortical	Hemorrhagic 16 × ischemic 13	NIHSS = 6.29	9 (31%)	0.56	1
Stagg et al. (2012)	1) 13; 2) 11(Note: 7 in both; 17 total)	64 years	Range 30–80 years	Cortical and subcortical	Hemorrhage 1; ischemic 16	Not mentioned	4 (23.5%)	37.90	1
Kakuda et al. (2011c)	11	61	13.7	Subcortical	hemorrhage 7; Ischemic 4	Brunnstrom Stage 3–5	5(45.4%)	69.90	0

(Continued)

Table 1 | Continued

Reference	Number of subjects	Age-mean	Age-SD	Cortical/ subcortical	Hemorrhagic versus ischemic	Stroke severity (mild/mod/severe)	Females (%)	Stroke duration (months)	Oxford quality scoring system
Madhavan et al. (2011)	9	65.4	13.2 (50–87 years)	Cortical and subcortical	Not mentioned	Lower extremity Fugl-Meyer 21–30 (maximum score 32)	4(44.4%)	130.80	0
Tanaka et al. (2011)	8	59.6	3.9	Subcortical	Not mentioned	Mixed based SIAS	4(50%)	21.10	1
Kakuda et al. (2011a)	5	61	56–66	Subcortical	Hemorrhage 4; ischemic 1	Brunnstrom Stage 3–5	2(40%)	64.00	1
Avenanti et al. (2012)	30	60.9 rTMS-PT; 64.0 PT-rTMS; 64.0 sham	8.8 rTMS-PT; 7.7 PT-rTMS; 12.1 sham	Cortical 3; corticosubcortical 1; subcortical 26	Hemorrhage 10; ischemic 20	Mild severity based on inclusion criteria	47%	31.47	3
Bolognini et al. (2011)	14	46.71	14.08	Cortical 9; corticosubcortical 5	Ischemic 12; hemorrhagic 2	Moderate to severe hemiparesis, per Fugl-Meyer (Stroke duration 35.21 ± 26.45)	64%	35.21	2
Conforto et al. (2012)	30	54.8 rTMS, 56.7 sham	11.7 rTMS, 14.8 sham	16 Subcortical, 14 cortical	Ischemic	Mixed; mild to sever per NIHSS (range 1–11) and FM (50–123)	40%	0.92	3
Hesse et al. (2011)	96	63.9 anodal tDCS; 65.4 cathodal tDCS; 65.6 sham	10.5 anodal tDCS; 8.6 cathodal tDCS; 65.6 sham	Mixed (cortical or corticosubcortical): 25 anodal tDCS, 24 cathodal tDCS, 26 sham tDCS. Subcortical 7 anodal tDCS, 8 cathodal tDCS, 6 sham	Ischemic	Severe per Upper extremity FM (7.8 ± 3.8 anodal tDCS, 7.9 ± 3.4 cathodal tDCS, 8.2 ± 4.4 sham; Stroke duration in weeks 3.4 ± 1.8 anodal tDCS, 3.8 ± 1.4 cathodal tDCS, 3.8 ± 1.5 sham)	39%	0.93	3
Mahmoudi et al. (2011)	10	60.8	14.1	Cortical 7, subcortical 3	Ischemic	Mild to moderate deficit (based on patients' ability to perform all items of Jebsen–Taylor Test (JTT)	30%	8.30	1
Nair et al. (2011)	14	55.8	(Range 40–76)	Cortical 9, subcortical 5	NA	Moderate to severe upper extremity impairment [per upper extremity Fugl-Meyer of 30.1 (±10.4)]	36%	30.50	2
Chang et al. (2012)	21	58.1 rTMS; sham 59.5	9.75 rTMS; 11.40 sham	Cortical 2, subcortical 15	3 Hemorrhagic, 14 ischemic	NA	41%	10.06	3
Hummel et al. (2005)	6	62.2	7.56	Subcortical	Ischemic	Mild (MRC4.8 ± 0.03)	33%	44.30	1

The phrases 'X' and NA denote unavailable information.

Table 2 | Inventory of motor assessment tools and reported outcome in selected transcranial Stimulation articles.

Reference	MRC	JTHF	HG	PF	PA	FM	PTT	sRT	cRT	MRs	NIHSS	FT	RGM	ASS	WMFT	ARAT	MA. Log	BBT	BIS	ASMI	LSMI	FAC	B	Others
Fregni et al. (2006)	B	#+	N	N	N	N	#+	#+	#+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Takeuchi et al. (2005)	N	N	N	ϕ	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mansur et al. (2005)	N	N	N	N	N	N	+	+	+	N	N	ϕ	N	N	N	N	N	N	N	N	N	N	N	N
Werhahn et al. (2003)	B	N	N	N	N	B	N	Δ	N	N	N	♦	N	N	N	N	N	N	N	N	N	N	N	N
Nowak et al. (2008)	B	N	N	N	N	N	N	N	N	B	B	+	+	N	B	N	N	N	N	N	N	N	N	N
Takeuchi et al. (2008)	N	N	N	#+	#+	B	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Dafotakis et al. (2008)	B	N	N	+	+	N	N	N	N	B	B	N	N	N	N	B	N	N	N	N	N	N	N	N
Kakuda et al. (2010b)	N	N	N	N	N		N	N	N	N	N	N	N	*	*	N	N	N	N	N	N	N	B	N
Liepert et al. (2007)	B	N	ϕ	N	N	N	ϕ	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Grefkes et al. (2010)	B	N	N	N	N	N	N	N	N	B	B	N	N	N	N	B	N	N	N	N	N	N	N	Written instructions on a monitor visible through a mirror whether to move the left, right, or both hands in the upcoming task-block (+)
Lotze et al. (2006)	B	N	N	N	N	N	N	N	N	N	N	Δ	N	N	N	N	N	N	N	N	N	N	N	N
Lomarev et al. (2007)	N	N	N	ϕ	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malcolm et al. (2007)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	ϕ	N	ϕ	ϕ	N	N	N	N	N	N
Khedr et al. (2005)	N	N	N	N	N	N	N	N	N	N	#+	N	N	N	N	N	N	N	#+	N	N	N	N	SSS#+

(Continued)

Table 2 | Continued

Reference	MRC	JTHF	HG	PF	PA	FM	PTT	sRT	cRT	MRs	NIHSS	FT	RGM	ASS	WMFT	ARAT	MA. Log	BBT	BIS	ASMI	LSMI	FAC	B	Others
Khedr et al. (2010)	N	N	*#	N	N	N	N	N	N	#	+	N	N	N	N	N	N	N	N	N	N	N	N	Shoulder abduction #; Dorsiflexion of toes Hip flexion#; Toe dorsiflexion# (only after 1 year fir 10 Hz)
Yozbatiran et al. (2009)	N	N	*	N	N	Ξ	*	N	N	N	N	N	N	N	N	ϕ	N	N	ϕ	N	N	N	N	Active ranges of motion at the affected side wrist and index finger metacarpophalangeal joint.
Ameli et al. (2009)	B	N	N	N	N	N	N	N	N	B	B	(+) And hand tapping +	N	N	N	B	N	N	N	N	N	N	N	N
Hummel and Cohen (2006)	B	N	N	+	N	B	N	+	N	N	N	N	N	B	N	N	N	N	N	N	N	N	N	N
Hesse et al. (2007)	*	N	N	N	N	*	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fregni et al. (2005)	B	+	N	N	N	N	N	N	N	N	N	N	N	B	N	N	N	N	N	N	N	N	N	N
Emara et al. (2010)	N	N	N	N	N	N	N	N	N	#+	N	+	N	N	N	N	N	N	N	N	N	N	N	Activity Index (AI) scale# +
Boggio et al. (2007)	B	#+	N	N	N	N	N	N	N	N	N	N	N	N	N		N	N	N	N	N	N	N	N
Pomeroy et al. (2007)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	ϕ	N	N	N	N	N	N	N	Peak torque about the elbow during isotonic concentric flexion/extension.

(Continued)

Table 2 | Continued

Reference	MRC	JTHF	HG	PF	PA	FM	PTT	sRT	cRT	MRs	NIHSS	FT	RGM	ASS	WMFT	ARAT	MA. Log	BBT	BIS	ASMI	LSMI	FAC	B	Others
Lindenberg et al. (2010)	B	N	N	N	N	# + UE	N	N	N	N	N	N	N	N	# +	N	N	N	N	N	N	N	N	For fMRI, performing repetitive elbow and wrist extension/flexion movements
Chang et al. (2010)	N	N	# +	N	N	(1) UE + (2) LL	N	N	N	N	N	N	N	N	N	N	N	ϕ	ϕ	# +	ϕ	ϕ	ϕ	N
Kim et al. (2010b)	B	N	N	N	N	#	N	N	N	B	B	N	N	N	N	N	N	N	ϕ	N	N	N	B	N
Kakuda et al. (2011b)	N	N	N	N	N	Ξ *	N	N	N	N	N	N	N	Ξ*	*	N	N	N	N	N	N	N	N	N
Kakuda et al. (2010a)	N	N	N	N	N	Ξ *	N	N	N	N	N	N	N	N	Ξ *	N	N	N	N	N	N	N	B	Ten seconds test X *
Koganemaru et al. (2010)	N	N	(A) + (after 30 min); (B) Ξ *	(B) Ξ *	N	N	N	N	N	N	N	N	N	(A) +; (B) Ξ *	N	N	N	N	N	N	N	N	N	(A) Active range of movement +(B) active range of movement X *; passive range of movement X *
Richards et al. (2006)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	ϕ	N	N	N	N	N	N	N	N	Motor Activity Log.3
Kim et al. (2006)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Finger motor task. (1) Movement accuracy (MA) + (2) movement time (MT) +
Khedr et al. (2009)	N	N	ϕ	N	N	N	# +	N	N	N	# +	# +	N	N	N	N	N	N	# +	N	N	N	N	Keyboard tapping#*
Takeuchi et al. (2009)	N	N	N	# +	# +	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mally and Dinya (2008)	N	N	N	N	N	Ξ *	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Score of spasticity at rest X *

(Continued)

Table 2 | Continued

Reference	MRC	JTHF	HG	PF	PA	FM	PTT	sRT	cRT	MRs	NIHSS	FT	RGM	ASS	WMFT	ARAT	MA. Log	BBT	BIS	ASMI	LSMI	FAC	B	Others
Kakuda et al. (2011d)	N	N	N	N	N	*	N	N	N	N	N	N	N	N	*	N	N	N	N	N	N	N	B	N
Kakuda et al. (2012)	N	N	N	N	N	Ξ *	N	N	N	N	N	N	N	N	Ξ *	N	N	N	N	N	N	N	B	N
Sasaki et al. (2011)	N	N	+	N	N	N	N	N	N	N	B	+	N	N	N	N	N	N	N	N	N	N	B	N
Stagg et al. (2012)	N	N	(1) Φ	N	N	N	N	(2) (+)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	(1) Response times (+); (2) choice response time condition (Φ).
Kakuda et al. (2011c)	N	N	N	N	N	*	N	N	N	N	N	N	N	N	*	N	N	N	N	N	N	N	B	N
Madhavan et al. (2011)	N	N	N	N	N	B	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Tracking a sinusoidal waveform (+)
Tanaka et al. (2011)	N	N	Φ	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	SIAS (B); MFKE(+)
Kakuda et al. (2011a)	N	N	N	N	N	* Ξ	N	N	N	N	N	N	N	*	* Ξ	N	N	N	N	N	N	N	N	N
Avenanti et al. (2012)	N	+#	=#	PG# +; force +	N	N	N	N	N	N	N	N	N	N	N	N	N	+#	N	N	N	N	N	NHPT +#
Bolognini et al. (2011)	N	+#	+	N	N	+	N	N	N	N	N	N	N	N	N	N	+#	N	N	N	N	N	N	N
Conforto et al. (2012)	N	+#	N	+	N	+	N	N	N	+	B	N	N	ϕ	N	N	N	N	N	N	N	N	N	N
Hesse et al. (2011)	+#	N	N	N	N	+#	N	N	N	N	N	N	N	+#	N	N	N	+#	+#	N	N	N	N	N
Mahmoudi et al. (2011)	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	B	

(Continued)

Table 2 | Continued

Reference	MRC	JTHF	HG	PF	PA	FM	PTT	sRT	cRT	MRs	NIHSS	FT	RGM	ASS	WMFT	ARAT	MA. Log	BBT	BIS	ASMI	LSMI	FAC	B	Others
Nair et al. (2011)	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Mean ROM shoulder abduction, elbow extension and wrist extension +
Chang et al. (2012)	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Sequential motor task – accuracy (MA) +
Hummel et al. (2005)	B	+	N	N	N	B	N	N	N	N	N	N	N	B	N	N	N	N	N	N	N	N	N	Hand ability B

JTHF, Jebsen–Taylor hand function test; MRC, Medical Research Council scale; HG, hand grip; PF, pinch force; PA, pinch acceleration; FM, Fugl-Meyer assessment, PTT, Purdue Pegboard test; sRT, simple reaction time test, cRT, choice reaction test, MRs, modified rankin score; NIHSS, National Institutes of Health Stroke Scale; FT, finger tapping (with different tasks); RGM, reach to grasp movement, ASS, Ashworth spasticity scale; WMFT, wolf motor function test; ARAT, action research arm test; MA.Log, motor activity log; BBT, box and block test; BIS, Barthel index scale; ASMI, arm score of motricity index; LSMI, leg score of motricity index; FAC, functional ambulatory category; B, Brunnstrom; SSS, Scandinavian stroke scale; UE, upper extremity; LL, lower limb; SIAS, stroke impairment assessment set; MFKE, maximal force of knee extension. (B) = apply in baseline only; (Δ) = negative; (Φ) = no significant change; (*) = positive, but no placebo control; (+) = positive; (#) = long-term positive; (Ξ) = long-term positive, but placebo control; (◆) = affect.

ADVERSE EFFECTS OF NON-INVASIVE STIMULATION

There was a large heterogeneity in the reporting of safety including different safety assessment tools and inclusion/exclusion criteria. There were no significant major safety events in the selected studies. Neurocognitive assessments as an index for safety were conducted in only a few of the studies (Fregni et al., 2006; Emara et al., 2010). None of the selected articles investigated mood changes following stimulation. Some of the articles have considered psychiatric illness as exclusion criteria (see Table S1 in Supplementary Material).

No major adverse effects have been reported. The side effects reported were tingling, headache, dizziness, itching, and increase in anxiety. In Fregni et al. (2006), one patient in the sham rTMS group reported an increase in the tiredness and another one noted a mild headache (Fregni et al., 2006).

Yozbatiran et al. (2009) showed a change in blood pressure of 7 mm Hg when assessing the effects of rTMS. We have noticed a variability of adverse effects in the articles. For the articles that did not specifically mention side effect, it should be noted absence of report does not imply absence of effect. These results are summarized in Table S1 in Supplementary Material.

Other measures of safety were used such as electroencephalography (EEG), which was as an exclusion criteria or a safety outcome. Studies using EEG as outcomes showed no changes in EEG post stimulation (Table S1 in Supplementary Material). Although rare, some subjects had dropped out of the studies because of adverse events. In Lomarev et al. (2007), one subject dropped out for not being able to tolerate the rTMS train at 100%. In Kim et al. (2010b), two patients discontinued treatment with tDCS; one due to headaches and the other due to dizziness. In Stagg et al. (2012), two patients withdrew from the study before completion: one due to claustrophobia and the other due to unrelated medical reasons. Both were noted to be unrelated to tDCS. These results are further listed in Table S1 in Supplementary Material.

EFFECTS OF GENDER ON BRAIN STIMULATION AND STROKE POPULATION

There was significant variability in number of male versus female patients in the selected articles. Information of individual analysis of motor effect per patient gender was unavailable for comparison. Therefore, aggregate analysis was conducted utilizing gender percentages (**Table 1**) per motor effect size. The mean male:female ratio was 63:37% of stroke patients in the selected articles. The analysis failed to find significant correlation; however there was a slightly positive trend for increased effect size as male percentage increased ($y = 1.0257x - 0.0117$. $R^2 = 0.0646$) and a conversely decreased correlation of effect size where the percentage of females were higher ($y = -1.0257x + 1.014$, $R^2 = 0.0646$).

STIMULATION PARAMETERS AND PROTOCOL

On review of selected articles, 36 (72.0%) used TMS as intervention, while 14 (28.0%) of the articles used tDCS stimulation. Most of the articles were designed with a strategy to decrease the contralateral hemisphere or increase the activity in the ipsilesional hemisphere (usually by increasing the activity of the peri-lesional area). Some articles utilized both paradigms. One important exception for this approach is the study by Mally and Dinya (2008)

Table 3 | Parameters for TDCS application parameters, placement, electrode Attributes, and employed placebo method.

Reference	Intensity (mA)	Duration (min)	Number sections	Location anode	Location cathode	Electrode (info and size)	Type of placebo	Concomitant therapy or motor tasks
Hummel and Cohen (2006)	1	20	1	Motor ipsilesional side	Contralateral Supraorbital	25 cm^2	30 s	N/A
Hesse et al. (2007)	1.5	7	30	Motor ipsilesional side	Contralateral Supraorbital	35 cm^2	No sham	Robot-assisted arm training
Fregni et al. (2005)	1	20	1	Ipsilesional side Or Supraorbital	Contralesional or supraorbital	35 cm^2	30 s	N/A
Boggio et al. (2007)	1	20	(1) 1 and (2) 5	(1) Ipsilesional side or supraorbital; (2) Supraorbital	(1) Contralesional side or supraorbital (2) contralesional side	35 cm^2	30 s	N/A
Lindenberg et al. (2010)	1.5	30	5	Motor ipsilesional side	Motor contralesional side	16.3 cm^2	30 s	Physical and occupational therapy
Kim et al. (2010b)	2	20	10	Ipsilesional side Or Supraorbital	Contralesional or Supraorbital	25 cm^2	60 s	Conventional, physical, and occupational therapy
Stagg et al. (2012)	1	(1) 20 (2) 10	1 session (3 total crossover)	Motor ipsilesional side or supraorbital	Motor contralesional side or supraorbital	35 cm^2	10 s (vertex)	N/A
Madhavan et al. (2011)	0.5	15	1 session (3 total crossover)	Motor ipsilesional side or contralesional (Leg)	Contralateral Supraorbital	8 cm^2 (anode) 48 cm^2 (cathode)	10 s	N/A
Tanaka et al. (2011)	2	10	1 session (2 total crossover)	Motor ipsilesional side (Leg)	Contralateral Supraorbital	35 cm^2 (anode) 50 cm^2 (cathode)	15 s	N/A
Bolognini et al. (2011)	2	40	10	Ipsilesional side	Contralesional side	35 cm^2	30 s	Constraint-induced movement therapy
Hesse et al. (2011)	2	20	30	Group A: ipsilesional side; Group B: contralesional side; sham: A or B set-up changing consecutively	Group A: contralateral orbit; Group B: contralateral supraorbit area; Sham: A or B set-up changing consecutively	35 cm^2	0 mA	Robot-assisted arm training
Mahmoudi et al. (2011)	1	20	1 session (5 total crossover)	Bilateral tDCS group: ipsilesional side; Anodal tDCS group: ipsilesional side; Cathodal tDCS group: contralateral supraorbital area; Extra-cephalic tDCS group: ipsilesional side; Sham tDCS group	Bilateral tDCS group: contralesional side; Anodal tDCS group: Contralateral supraorbital; Cathodal tDCS group: contralesional side; Extra-cephalic tDCS group: contralateral deltoid muscle; Sham tDCS group: Not listed	35 cm^2	30 s	N/A
Nair et al. (2011)	1	30	5	Contralateral supraorbital area	Contralesional	NA	Stimulation intensity turned off at unspecified interval	Occupational therapy
Hummel et al. (2005)	1	20	2	Ipsilesional	Contralateral supraorbital	25 cm^2	30 s	N/A

Table 4 | rTMS parameters, application location, duration of treatment, and placebo implementation.

Reference	TMS type	Frequency	Intensity % motor threshold	Number of stimuli per train	Type of placebo or active control	Concomitant Therapy or motor tasks
Fregni et al. (2006)	Contralesional	1 Hz	100%	1200	Sham coil	N/A
Takeuchi et al. (2005)	Contralesional	1 Hz	90&	1500	90°	N/A
Mansur et al. (2005)	Contralesional	1 Hz	100%	600	Sham coil	N/A
Werhahn et al. (2003)	(1, 2, and 4) Contralesional and Ipsilesional (3) Ipsilesional	(1) Single (2) 1 Hz; (3) 1 Hz; (4) single	(1) 130%; (2) 150%; (3) 150%; (4) 130%	(1) *x*; (2) 5; (3) 1800 (4) *x*	Vertex (control stimulation)	N/A
Nowak et al. (2008)	Contralesional	1 Hz	100%	10	Vertex (control stimulation)	N/A
Takeuchi et al. (2008)	Contralesional	1 Hz	90%	1500	90°	N/A
Dafotakis et al. (2008)	Contralesional	1 Hz	100%	600	Vertex (control stimulation)	N/A
Kakuda et al. (2010b)	Contralesional	1 Hz	90%	1200	No sham	Intensive occupational therapy (OT)
Liepert et al. (2007)	Contralesional	1 Hz	90%	1200	Sham coil	N/A
Grefkes et al. (2010)	Contralesional	1 Hz	100%	600	Vertex (control stimulation)	N/A
Lotze et al. (2006)	Contralesional	20 Hz	120%	3	90°	N/A
Lomarev et al. (2007)	Ipsilesional	20 and 25 Hz	110, 120, and 130%	10 and 20	90°	N/A
Malcolm et al. (2007)	Ipsilesional	20 Hz	90%	40	Attaching surface electrodes underneath the magnetic coils and in contact with the scalp connected to the electromyography	Constraint-induced therapy
Khedr et al. (2005)	Ipsilesional	3 Hz	120%	30	Coil angled away from the head	Continued to receive their normal therapy
Khedr et al. (2010)	Ipsilesional	3 and 10 Hz	(1) 130%; (2) 100%	Group (1) 14, Group (2) 20	Coil angled away from the head	combination with conventional therapy
Yozbatiran et al. (2009)	Ipsilesional	20 Hz	90%; and 7 patients 60% device output	40	No sham	N/A
Ameli et al. (2009)	Ipsilesional	10 Hz	80%	50	Vertex (control stimulation)	N/A
Emara et al. (2010)	Contralesional and ipsilesional side	1 and 5 Hz	80–90% ipsilesional 110–120% contralesional	(1) 750 pulses; (2) 150 pulses	90°	received standard physical therapy
Pomeroy et al. (2007)	Ipsilesional	1 Hz	120% MT	40	Sham coil	Voluntary muscle contraction (real and placebo) They were asked to flex and extend the paretic elbow and to continue to repeat or to attempt this for 5 min

(Continued)

Table 4 | Continued

Reference	TMS type	Frequency	Intensity % motor threshold	Number of stimuli per train	Type of placebo or active control	Concomitant Therapy or motor tasks
Chang et al. (2010)	Ipsilesional	10 Hz	90%	1000	90°	Motor practice consisted of 50 s of reaching and grasping exercises, which were conducted after each rTMS. Plus conventional, physical, and occupational therapy
Kakuda et al. (2011b)	Contralesional	1 Hz	90%	1200	90°	Occupational therapy
Kakuda et al. (2010a)	Contralesional	1 Hz	90%	1200	No sham	Occupational therapy
Koganemaru et al. (2010)	Ipsilesional	5 Hz;	100% of the active motor threshold	(1) 600; (3) 7200	(1) Sham coil; (3) no sham	Exercises for the extensors of the wrist and fingers
Richards et al. (2006)	Ipsilesional	20 Hz	90%	2000	Surface electrodes under the magnet sham rTMS	Constraint-induced movement therapy
Kim et al. (2006)	Ipsilesional	10 Hz	80%	20	90°	N/A
Khedr et al. (2009)	Contralesional and ipsilesional side	(1) 1 Hz; (2) 3 Hz	(1) 100%; (2) 130%	900 pulses	Coil angled away from the head	conventional therapy
Takeuchi et al. (2009)	(1) Contralesional; (2) ipsilesional; (3) bilateral	(1) 1 Hz; (2) 10 Hz; (3) 1 and 10 Hz	90%	(F1) 1000; (F2) 1000; (F3) 2000	90°	N/A
Mally and Dinya (2008)	Contralesional and ipsilesional side	1 Hz	(30% of 2.3 T)	100	No sham	N/A
Kakuda et al. (2011d)	Contralesional	1 Hz	90%	1200	No sham	Intensive occupational therapy (OT)
Kakuda et al. (2012)	Contralesional	1 Hz	90%	1200	No sham	Intensive occupational therapy (OT)
Sasaki et al. (2011)	Contralesional or ipsilesional side	(1) 1 Hz or (2) 10 Hz	90%	1800 or 1000	90°	N/A
Kakuda et al. (2011c)	Contralesional	6 Hz (priming per 10 min) + 1 Hz per 20 min	90%	600 + 1200 = 1800	No sham	Intensive occupational therapy (OT)
Kakuda et al. (2011a)	Contralesional	1 Hz	90%	1200	No sham	Intensive occupational therapy (OT) + Levodopa
Avenanti et al. (2012)	Contralesional	1 Hz	90%	1500 pulses (1 train)	90°	physical therapy
Conforto et al. (2012)	Contralesional	1 Hz	90%	1500 pulses (1 train)	90°	Therapies to outpatient customary rehabilitation,
Chang et al. (2012)	Ipsilesional	10 Hz	80%	50 pulses × 20 trains × 10 daily sessions = 10,000 total	90°	N/A

**Values for each experiment group are separated by bracketed numbers. For example, if an experiment has three groups, the information per group is listed as (1), (2), and (3), respectively.*

that demonstrated motor improvement by inhibiting the perilesional region. However, it is also important to note that there was no placebo control included here. We have summarized the different protocols in **Tables 3** and **4**.

SHAM: UTILIZATION OF PLACEBO STIMULATION

All the tDCS studies used the same type of sham procedure, which was a brief initial stimulation to produce a tingling sensation followed by decreasing the administration to zero. However, they varied by the duration of initial stimulation, which was 30 or 60 s. The protocols were primarily based on three different strategies: the use of (1) cathodal stimulation in the unaffected hemisphere, (2) anodal in the affected hemisphere, (3) or both anodal and cathodal stimulation applied simultaneously. These three strategies are based on the inter-hemispheric interaction theory described above. The different rTMS parameters, stimulation strategy, and sham type are listed in the **Table 4**.

Most of the rTMS studies had used sham stimulation or active control stimulation (77.7%), but the techniques used were different; especially in the type of coils and cortical targets used (**Table 4**). All utilized an rTMS coil but using different approaches: (1) active coil placed on the vertex; (2) active coil, with an angle of application of 90°; (3) sham coil, which induces no magnetic field.

FAILURE OF IMPROVEMENT: MOTOR OUTCOMES COMPARED TO PLACEBO

A majority of the results was positive for increased improvement compared to placebo, with the exception of three articles (Lomarev et al., 2007; Malcolm et al., 2007; Pomeroy et al., 2007). For the Lomarev et al. (2007) study, results were mixed with some outcomes showing positive results (Lomarev et al., 2007). An important distinction was that the Lomarev et al. (2007) study was primarily implemented to assess safety, while the Pomeroy et al. (2007) study was predominantly designed to test the feasibility of the new methodology (Lomarev et al., 2007; Pomeroy et al., 2007).

Although the article Werhahn et al. (2003) also showed that rTMS induced no improvement or worsening, this study had the main aim of inducing a "Transient, Virtual, Reversible Lesion" to better understanding motor recovery (Werhahn et al., 2003). Another study showing impairment in motor function was the Lotze et al. (2006) study that used rTMS as interference while assessing fMRI data. These results may be secondary to the employment of TMS for inhibition rather than facilitation of motor networks.

MOTOR EFFECTS SIZE

In our assessment of the magnitude of effect size, we found an overall improvement in motor outcome (**Figure 1**). Most of the studies used small sample sizes. The results from the fixed effects model revealed a significant pooled effect size of 0.584 (95% CI, 0.440, 0.729; **Figures 1** and **2**). The random effects model showed similar results 0.590 (pooled effect size, 95% CI, 0.421, 0.760). Using the Begg and the Egger test for the analyzed trials, we found no evidence of publication bias and the distribution of studies was symmetrical with non-significant *p*-values (**Figure 3**). This suggests that the results are not related to a publication bias. Of note, there were no negative results with tDCS.

LONG-TERM FOLLOW-UP

There is a subset of the selected articles that performed long-term follow-up. The time of follow-up varied from 30 min (Takeuchi et al., 2005) to 1 year (Khedr et al., 2010). Khedr et al. (2010) showed a long-term effect lasting 1 year. It is noted in this article that the rTMS was applied in the acute phase of stroke. In the article Yozbatiran et al. (2009), the Fugl-Meyer (FM) did not reveal a difference immediately post-rTMS stimulation, but showed difference 1 week later. In the article Kim et al. (2010b), FM did not demonstrate a difference 1 day after cathode tDCS, but showed a difference 6 months later.

DISCUSSION

This review of the transcranial stimulation articles includes data from 50 articles, assessing 1314 (1282 stroke patients and 32 healthy) subjects. In summary, the data suggest the use of non-invasive brain stimulation in stroke population is associated with improvements of motor outcomes. There was significant heterogeneity of patient population characteristics, intervention parameters, and selected assessments.

STUDIES RETRIEVAL

Though the yearly number of studies did not vary significantly, there was an overall increase in publications over time (years) that peaked in 2011. The publications averaged at 4.9 articles per year. In order to attain a larger perspective, we compared this trend with a trajectory of the overall trend of non-invasive articles publications. The comparative trend was obtained from a PubMed search utilizing the search terms of "stroke" and "transcranial stimulation" until the publication year of 2011. Of note, the comparison trend used data searched until the end of December of 2011 in order to provide a clear trend for the whole year of 2011. When assessing for tDCS alone (utilizing the same search terms and "tDCS" or "direct"), the data also demonstrated an increase in publications from its 0 to 2 yearly publication rate to recently 47 articles for 2011 (a 235% increase from PubMed publications of 2002). Lum et al. (2002) reports that the increased drive for novel therapies in stroke rehabilitation is indirectly actuated by an emerging cost-reduction emphasis in healthcare. Other articles also support this hypothesis by proposing a socioeconomic justification for the search for new stroke therapies (Edwards and Fregni, 2008; Nowak et al., 2009). The increasing popularity of novel therapies is suspected to be due to the sustained impact of chronic disability in stroke (Lum et al., 2002; Edwards and Fregni, 2008; Nowak et al., 2008). This observation is supported across the literature, as other sources have noticed that both tDCS and rTMS are experiencing an emerging popularity of use in the field of medicine and research (Ryan et al., 2006; Harris et al., 2008; Funke and Benali, 2011; Schwarzkopf et al., 2011; Fox et al., 2012; Hellmann et al., 2012). Ratan and Noble (2009) argues for the need for infrastructural support to facilitate development and translation of novel therapies. Kent et al. (2009) also suggests advocacy for use of advanced technology to develop models between neuroplasticity and learning in stroke recovery. In summary, the field of medical research suggests that the field of non-invasive stimulation is an emerging field with a potential role in stroke rehabilitation.

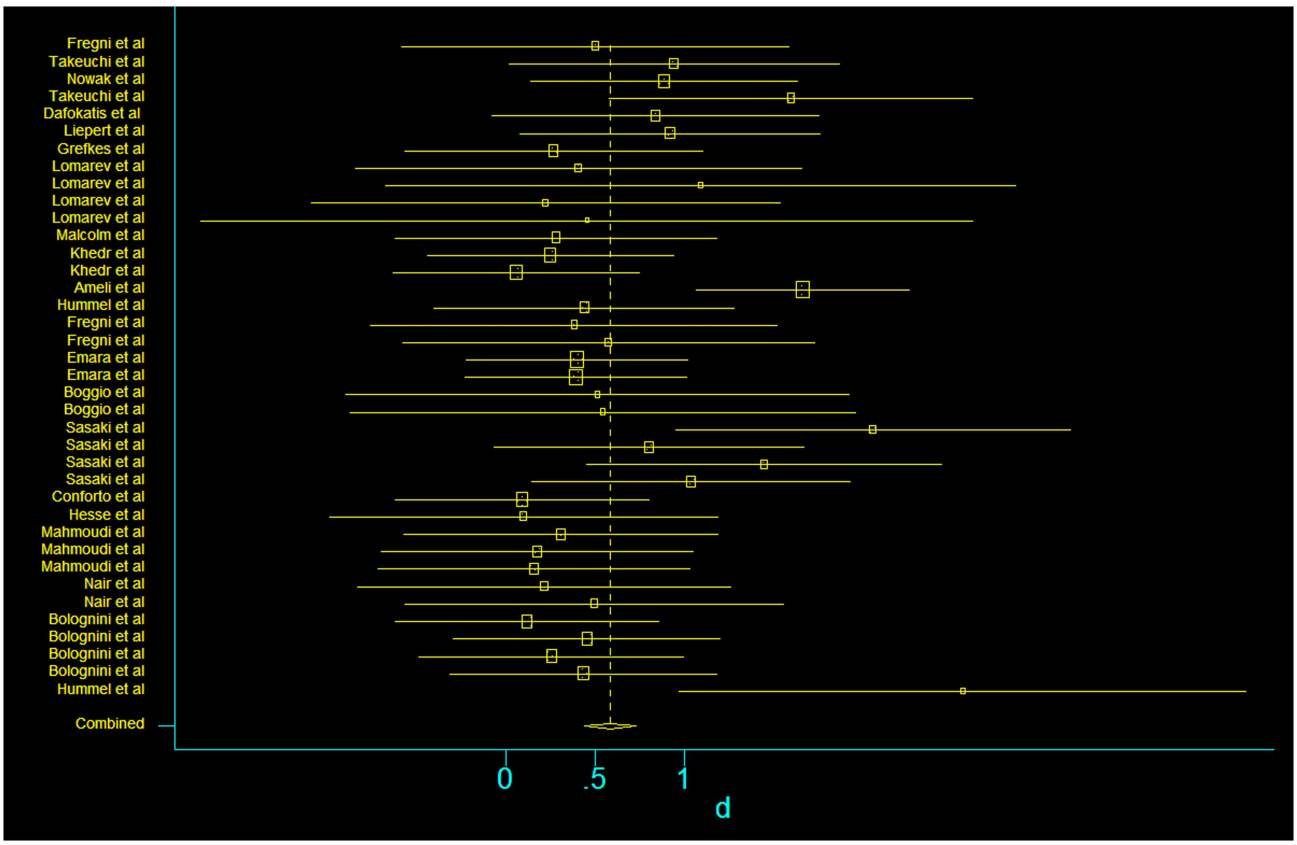

FIGURE 1 | Forest plot of the subset of studies with amenable and data-available for systematized comparison, with the pooled effect size for studies of transcranial stimulation on motor.

EFFECTS OF AGE ON BRAIN STIMULATION AND STROKE

In regards to age, the average age of this systematic review was 58.46, which is a low average when compared to the general stroke population. A comparison to the other reviews of stroke in the literature reveals a meta-analysis of therapy and stroke that reports older patient averages to be 65.3–74.7 years for their respective treatment groups (Craig et al., 2010). Investigation of the study design of our selected articles demonstrates that this finding is not attributed to the inclusion/exclusion criteria or adverse events (Table S1 in Supplementary Material). Of note, a recent review of non-invasive stimulation established an average patient age of 58.77 (Richards et al., 2008), a report similar our age finding.

Given that certain articles have discussed safety concerns with extremities of age, we considered whether the average age was related to safety concerns (Quintana, 2005). Since age did not correlate with safety reports in these articles. A potential explanation is an increased utilization of new treatments in the younger stroke population (Luker et al., 2011). This trend is substantiated by a recent review of stroke management, where age is evidenced to be a significant determinant of type of post-stroke care (Luker et al., 2011). Furthermore, according to the TMS guidelines, age does not increase the risk of adverse events in the utilization of TMS.

We analyzed the relationship between effect-size of motor outcomes after non-invasive stimulation with age. We noticed no correlation ($r = 0.279$, $p = 0.0984$) between age and effects size when using a linear regression model. The Pearson coefficient was very low and the p-value was high, which conveys a poor association and low significance. A comparison of effect sizes of patients above and below the median age (55.9) also failed to reveal a significant difference in age groups and motor outcomes (Mann–Whitney U-test: p-value 0.101694, two-tailed test.) Sub-analysis of age by rTMS and tDCS articles also failed to show a significant difference (Mann–Whitney two-tailed U-tests: rTMS $p = 0.1246498$, tDCS $p = 1$). We conclude that our analysis was unable to find a difference or association in effect sizes of motor outcomes when analyzed by age.

Future studies would be helpful in further exploring this concept of age and motor outcomes in transcranial stimulation. Literature suggests that there exists an increased level of neuroplasticity in younger population (Pinto et al., 2012). This may be an important consideration in transcranial stimulation of stroke patients to determine if younger patients would experience increased motor improvements. Some data suggests that younger patients may experience greater improvement based upon an increased ability of the contralateral hemisphere to compensate for the stroke lesion (Ipek et al., 2011). Studies should explore whether the level of cerebral atrophy in the setting of older age should be a consideration for analyzing age-related motor effects (Nahas et al., 2004;

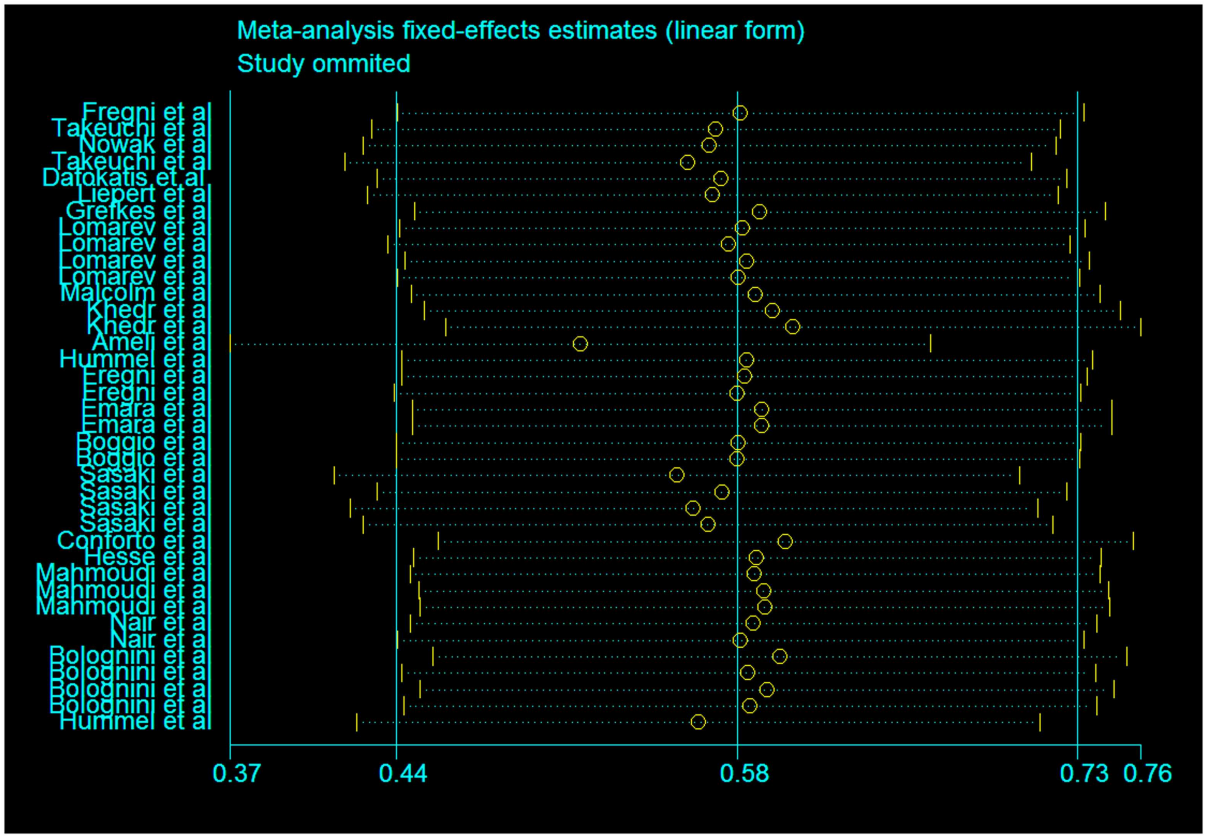

FIGURE 2 | Assessment of the fixed effects size estimates in linear form with effect size as Cohen's *d* (standard mean difference) and employing error bars to represent the 95% confidence interval.

Decarli et al., 2012). Further studies are needed to explore fully the relationship between age and motor outcome after transcranial stimulation in stroke patients.

EFFECTS OF GENDER ON BRAIN STIMULATION AND STROKE POPULATION

The analysis failed to find significant correlation; however there was a slightly positive trend for increased effect size as male percentage increased and a conversely decreased correlation of effect size where the percentage of females were higher. In comparison with the literature, a study on chronic tinnitus with tDCS demonstrated an opposite trend with females improving more than males (Frank et al., 2012). Another study in tDCS on behavior modification and reasoning also found an increased effect in women (Fumagalli et al., 2010). Furthermore, a study of temporal cortex tDCS on its effects on facial expression recognition also noticed increased effects and modulation of the cortex with females (Boggio et al., 2008).

Overall, the findings of this review did not provide sufficient information to draw definitive conclusions on the effects of gender. Results may be related to statistical sampling and analysis. An explanation for why the results failed to find increased effects with female-predominant articles is that the findings are masked by the uniqueness of stroke epidemiology compared to the other diseases studied in other articles. As described above, the average patient age of this study was 57. According to the AHA, men tend to have more strokes at an earlier age than women do (Lloyd-Jones et al., 2009). Ergo, one would expect fewer females in our articles. This decreased number of females may be relatively too few (in comparison to the male patients) to demonstrate a preferential improvement in motor outcome. This epidemiological trend of more males than females is supported in this review's high male:female ratio of 63:37%. The variability in number of male versus female patients in these articles may also be due to varying recruitment or level of desire/comfort with neuromodulation treatment. Once again, it should also be emphasized that there are no contraindications against non-invasive stimulation for either gender (Rossi et al., 2009). Further studies should assist in delineating this effects of stimulation in gender, as some articles report there is a differential effect (Knops et al., 2006; Boggio et al., 2008; Chaieb et al., 2008). This information may prove paramount in helping to individualize stimulation treatment.

THE IMPACT OF THE CHRONICITY OF STROKE ON THE RECOVERY OF MOTOR FUNCTION

As listed above, there is significant variability in the phase of stroke for which the patient received the stimulation between the articles. This variability of time after stroke also exists between subjects

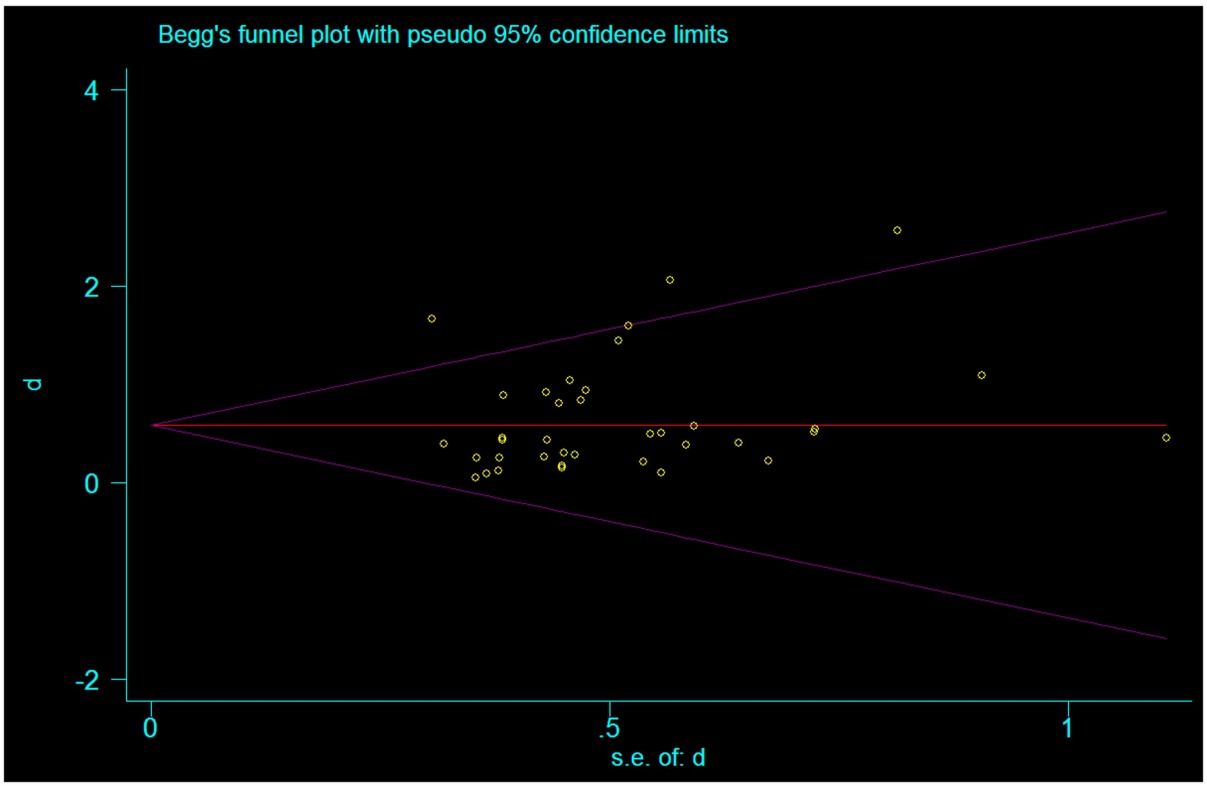

FIGURE 3 | Funnel plot representing publication bias assessment of the effect sizes (Cohen's *d*) by accounting for their standard errors. The pooled effect size is represented by the horizontal solid line. The 94% confidence interval expected for each is represented by the diagonal lines. (Of note, this graph assumes no heterogeneity between studies.)

within the articles. This variability may be more meaningful when it is related with acute/subacute stroke than the ones related to chronic stroke. One specific issue we noticed in the articles is that overall, there was no consensus as to what was considered acute, subacute, or chronic stroke. We further discuss some solutions below.

The articles that applied stimulation in patients within approximately 1 month or less after stroke demonstrate significant heterogeneity in post-stroke duration, both intra and inter-study: Liepert et al. (2007), 7.3 days (SD: 4.5); Khedr et al. (2010), 6.5 days (SD: 3.63); Khedr et al. (2005), 7.1 ± 1.4 days for active stimulation and 7.3 ± 1.5 days for sham; Chang et al. (2010), 13.4 days with range 7–26 (12.9 ± 5.2 days for active stimulation, 14.4 ± 5.9 days for sham); Khedr et al. (2009), 17.1 days (SD: 3.6); (Kim et al., 2010b), 34.0 ± 27.1 for anodal tDCS, 19.4 ± 9.3 for cathodal tDCS, and 22.9 ± 7.5 for sham; Sasaki et al. (2011), 18.4 ± 5.8 days for high-frequency rTMS, 17.0 ± 6.0 days for low frequency rTMS, 15.4 ± 4.3 days for sham; Hesse et al. (2011), 23.8 ± 12.6 for anodal tDCS, 26.6 ± 9.8 for cathodal stimulation, and 26.6 ± 10.5 days for sham; Conforto et al. (2012), 27 ± 8.6 days for active stimulation and 28.3 ± 10.5 days for sham stimulation (Khedr et al., 2005, 2009, 2010; Liepert et al., 2007; Chang et al., 2010; Kim et al., 2010b; Hesse et al., 2011; Sasaki et al., 2011; Conforto et al., 2012).

This may further serve as a confounding factor, as the responses may differ with this variance. In these articles, the stimulation paradigms were employed with approaches based upon the interhemispheric theory. However, there are other mechanisms of neuronal recovery that may be applicable and worth consideration.

For instance, it is suspected that the NMDA receptor may play an important role in acute phase, in preventing neuronal death in the penumbra area. There is a theory that postulates a possible bipartite capacity of NMDA receptor after the stroke: (1) it is possible that in the early stage after stroke the overactivation of NMDA seems to be detrimental; (2) on the other hand, in a delayed phase this activation may be essential for neuronal recovery (Lo, 2008).

Since, tDCS and TMS seems to have effects on the NMDA receptors (Kim et al., 2010a), further studies are necessary to define the best moment to alter NMDA activity after stroke. Studies may then use this data to decide the best application for these neuromodulatory techniques. It is possible that the best approach is to use low frequency rTMS and cathode tDCS in the hyperacute/early phase and high-frequency rTMS and anodal tDCS in the chronic/later phases.

This suggestion is in light of a theory that rTMS may increase brain metabolism (Valero-Cabre et al., 2007), which may be harmful for the penumbra area. On the other hand, there is evidence that rTMS may decrease apoptosis after stroke (Gao et al., 2010). Gao et al. (2010) has shown that high-frequency rTMS therapy increased glucose metabolism and inhibited apoptosis in the ischemic hemisphere of a rat model of transient cerebral ischemia.

Similarly, Yoon et al. (2011) has demonstrated a role of diminishing apoptosis in the 20 cerebral ischemic rats after a 10-Hz frequency were applied to the ipsilesional cortex at day 4 after cerebral ischemia. Considering this evidence, a conservative approach would be to opt for low frequency rTMS in contralateral hemisphere like Liepert et al. (2007) since it circumvents increasing brain metabolism by avoiding direct action on the penumbra area. These parameters may provide a more protective effect.

The question that remains is how such an intervention will alter the trajectory of the stroke over time. It appears that this can alter the natural recovery of the stroke, as evidenced by Khedr et al.'s (2010) improvement at 1-year follow-up.

The lack of consensus in definition of acute versus chronic phases of stroke is one of the main issues in post-stroke duration. Without a standardization of this description, analysis, and generalizations of implications are going to be limited in the future. Perhaps maintenance of a stringent classification system would facilitate studying the safety and other effects of stimulation, as well as the time course of neuroplasticity. Although none of the articles demonstrated worsening motor function during the acute phase, the question remains whether this is safe to perform during the acute phase. There were not enough acute articles included in the effect size analysis to obtain a difference in the acute versus chronic stage. However, we continue to raise the question of whether (and how) the strategy during acute phase should differ. Overall, we contemplate as to whether implementation of neuromodulation during the acute period will block maladaptive plasticity. Perhaps it would also enhance beneficial plasticity and early recovery. Yoon et al. (2011) article supports this use by demonstrating the role of diminishing apoptosis in the post-stroke period.

In this regard, we suggest using the definition of Bahn et al. (1996) of stroke stages: hyperacute: the first six post-ictal hours; acute: 6–24 h; subacute: 24 h to 6 weeks; chronic: greater than 6 weeks. By this classification, this would make all the selected articles, subacute and chronic. Perhaps employment of this system will help with standardization. Overall, we anticipate that this will be an exciting area of research and development in the future.

EFFECT OF THE MAGNITUDE AND NATURE OF THE STROKE ON MOTOR OUTCOME: STROKE SEVERITY AND LOCALIZATION

There was significant heterogeneity in the severity of strokes reported in the articles. **Table 1** shows the severity of strokes listed. We question whether the severity of stroke provides better or worse potential for neuroplasticity, or if this issue confounded by the ability to measure response. There are stroke articles that demonstrate significant improvement even with markedly severe strokes, which helps illustrate that the mechanism is effective. Specifically, we refer the reader to a case report that evinces post-stimulation improvement of a severe stroke subject (Boggio et al., 2006). This aspect requires further delineation in the future studies by standardization of the level of stroke in study participants.

The trend of heterogeneity of study population continues in the localization of the stroke. This is also delineated in **Table 1**. Out of the articles analyzed for effect size, there were eight results that studied subcortical strokes, while the remaining effect sizes were articles using both cortical and subcortical stroke. The analysis demonstrated a highly significant increased effect size when stimulation was applied to subcortical strokes versus the mixed strokes ($p = 2.45598e{-}05$, two-tailed Mann–Whitney U-test.) When sub-analyzed within the context of type of stimulation technique, this significant finding was reproducible for both rTMS and tDCS articles (rTMS $p = 0.01115294$ and tDCS $p = 0.01428572$, Mann–Whitney two-tailed U-test). The increased effect size in articles with subcortical strokes leads to an interesting point. As described in the introduction, one of the primary observations that made non-invasive stimulation of stroke patients worthy of discussion was based on changes in cortical excitability. In essence, the neuroimaging findings of cortical excitability and other descriptions of inter-hemispheric inhibition (Hummel and Cohen, 2006) are all observations that occur in the neuronal cortex. Therefore, it is possible that the subcortical strokes preserve the cortex and allow neuroplasticity and neuroadaptation of the post-stroke maladaptive changes. This explanation may be the main component underlying the improvement in the subcortical patients. In corroboration, it is notable that one of the selected articles also supports this finding, by describing greater improvement with subcortical versus cortical stroke (Ameli et al., 2009). If this is a re-demonstrable finding, then it may be possible to utilize stroke localization in the future as a means of treatment stratification and perhaps even a predictor of response.

ADJUVANT THERAPY

The adjuvant therapy results are listed in **Tables 3** and **4**. There was insufficient data to analyze the type, order, and effect of adjuvant therapy on motor effect size. We contemplate whether the sequence of stimulation and adjuvant therapy interfered with the results. Specifically, does implementing therapy pre-, post-, or co-stimulation affect the overall motor effect? Perhaps therapy provides a priming effect, or conversely interrupts the neuromodulatory learning. An interesting point of consideration especially with negative studies is whether the adjuvant therapy is the limiting factor influencing the observed results. Is there an underlying type II error present? It may be that there is a ceiling effect on motor improvement achievable after stroke for some patients. In those cases, it may be that the therapy increases the outcomes to the ceiling, thereby making it impossible to detect any further improvement that would have been attained from the stimulation application. There are few articles that compare constraint induced therapy and rTMS (Richards et al., 2006; Malcolm et al., 2007) but were unable to establish a difference. However, with tDCS, it has been demonstrated that tDCS has an additional benefit when applied on top of constraint induced therapy in healthy (Williams et al., 2010) and stroke subjects (Bolognini et al., 2011).

ADVERSE EFFECTS AND SAFETY CONSIDERATIONS IN THE IMPLEMENTATION OF NEUROMODULATION

These articles highlight certain concerns previously raised regarding the safety parameters of rTMS. Recent articles advocate for higher doses of rTMS application in order to optimally define the most efficacious paradigm (Hadley et al., 2011). Current safety protocols that guide treatment are based on ascertaining the spread of cortical activity after stimulation in healthy patients (Pascual-Leone et al., 1993; Rossi et al., 2009). Studies such as Benninger et al. (2009) have shown doses as high as 50 Hz have been safely

administered in the Parkinson's population. However, it is imperative to determine how this spread of cortical activity will be altered in stroke patients.

A cardinal reason that dose optimization must occur in the stroke population is the potential for epileptogenic events (Burn et al., 1997; Rossi et al., 2009) According to Olsen (2001), compared to the general population, the risk of developing seizures is 35 times more likely in the stroke population in the first year after stroke and 19 times more likely in the second year after stroke. Another study documents the risk of seizure as 23 times more likely the first year of stroke and remained increased over the following three post-stroke years (So et al., 1996). Out of the selected articles, one article noted a spread of electromyographic activity, denoting a possible peripheral manifestation of cortical-excitation spread, as per the suggestion of the Pascual-Leone et al. (1993) article (Pascual-Leone et al., 1993; Lomarev et al., 2007). Lomarev et al. (2007) further suggests the safety parameters may be different for healthy and stroke subjects. Therefore, for patients with additional risk, rigorous monitoring is still critical (Rossi et al., 2009).

Given the aforementioned guidelines of cortical activity were initially based on healthy subjects, it is still to be determined the exact dose that will elicit a spread of cortical activity in stroke patients. Specifically, it will be imperative to determine the stimulation parameters and the stroke subtype characteristics for which they are applicable. For example, there exists concern that the ischemic region of the stroke might be more epileptogenic than healthy tissue, thereby increasing the need for vigilance during stimulation. Although the overall cause of epileptic seizures is poorly understood, Olsen (2001) offers that the substrate of the seizure is likely attributed to the ischemic penumbra surrounding the stroke lesion. The enhanced release of excitotoxic glutamate, disintegration of membrane material, ionic disruption, and release of inter-neuronal substance is also implicated (Olsen, 2001). Hemorrhagic stroke subtypes are described as being more epileptogenic (Kilpatrick et al., 1990; Reith et al., 1997). In the 1997 Copenhagen Stroke Study, post-stroke seizures were found to be more common in the hemorrhagic group than the ischemic stroke group (Reith et al., 1997). Furthermore, Bladin et al. (2000) also describes how stroke type (ischemic versus hemorrhagic) impart different seizure risk. Burneo et al. (2010) also lists stroke severity and presence of hemorrhage as risk factors for seizure after stroke by multivariate analysis. Within our selected article group, there are articles that consider this caution by excluding patients with hemorrhage due to suspected increased risk of seizure (Carey et al., 2008). It is worth consideration that the presence of hemorrhage may require specific safety recommendations in the future.

An additional consideration is that some studies note that hemorrhagic stroke occurred exclusively in patients with cortical involvement of the stroke territory (Kilpatrick et al., 1990). This may imply a safety rationale for different stimulation protocols for cortical versus subcortical strokes.

These above considerations make it evident that further consideration and a more in-depth discussion of the stroke characteristics may be warranted for tailoring and development of future stimulation protocol. Furthermore, as the doses of high-frequency rTMS are advanced in the future, acquisition of studies as performed in the stroke population will be warranted to establish supporting safety data (Lomarev et al., 2007). In the interim, many options using modalities of low and moderate frequency rTMS exist to explore their role on neurorecovery of motor function.

One should note however that although seizure events are highly discussed, there have been none reported in this current literature group. It should also be noted historically that the seizure events that have been reported in TMS history have been frequently associated with secondary causes such as medications, past medical history, environmental factors, outside of the TMS alone. In fact, according to recent rTMS guidelines by Lefaucheur et al. (2011), most of the reports in the literature were secondary to parameters that did not previous recommendations or concomitant use of medications that lowered the seizure threshold. However, for the sake of prudence, seizures should continue to be kept high on the differential of concerns when discussing safety. Though the use of psychotropic medications has been reported to increase the risk of seizure (Rossi et al., 2009), it is undetermined how many of these medication warrant exclusion as an official exclusion criteria. Table S1 in Supplementary Material indicates that only few articles considered these criteria. Furthermore, some of these articles contend that the exclusion of these medications was not for safety reasons but rather for quality outcomes, to avoid medication interference with the results.

Other safety concerns peri-stimulation include changes in cognition and mood. Although this adverse event was not reported in the selected articles, it is worth noting that most of them did not measure for them. This is an interesting omission considering the FDA approval for rTMS use for is for depression which is a mood disorder (Dell'osso et al., 2011). Consequently, this alone should provide sufficient incentive to include this category in the safety outcomes in stimulation studies. Specifically, it would be beneficial to ascertain how stroke location, severity, and choice of stimulation parameters affect the outcomes. Future studies would be helpful in discriminating these issues.

Further studies should also explore the ideal safety-monitoring device, whether it be EEG or development of specific biomarkers. Before implementation, one should considering referencing multiple sources of safety reviews of tDCS and TMS treatments (Rachid and Bertschy, 2006). Certain articles compare TMS field distributions for healthy versus stroke tissue (or atrophy or tumor), noticed modified current density distributions and alterations for stimulation proximal to the stroke (Mansur et al., 2005; Wagner et al., 2008). Safety guidelines also suggest that further EEG studies are needed to collect data on various parameters on stimulations (Rossi et al., 2009). Overall, further studies analyzing the effects of protocols using high-frequency rTMS would be helpful in determining specialized safety parameters in order to individualize recommendations for high versus low frequency rTMS.

STIMULATION PROTOCOL AND PARAMETERS

There were multiple variations of parameters employed in the selected studies, mostly to improve inter-hemispheric imbalance (with the exception of Mally and Dinya, 2008). Mally and Dinya (2008) given that some of the articles selected motor as a secondary (rather than primary) outcome, it is possible that they selected parameters that were more efficiently measured in a single session of stimulation. In comparison, certain articles such as Fregni

et al. (2006) report that repeated sessions are helpful in maintaining efficacy. Therefore, one can expect some heterogeneity in the implications of the results attained.

The concept of inter-hemispheric interaction and balance is further considered in most of the selected studies (as described above). This hypothesis is a prevailing theory in the field and is reinforced by certain studies such as Werhahn et al. (2003). However, we contemplate in our review whether the contra-lesional hemispheric hyperactivity denotes an additional purpose. Specifically, Lotze et al.'s (2006) investigation demonstrates where stimulation of contra-lesional hemisphere can contribute to further impairment of the paretic hand. It is to be considered that the hyperactivity in the contra-lesional hemisphere may be beneficial in a small particular subset of strokes. This may be specific for subjects with complete motor recovery. The implication may be that stimulation protocols should be individualized to the level of recovery, especially in this subset of stroke patients.

The second consideration regarding the inter-hemispheric interaction theory is the role of the healthy hemisphere. There are some articles that propose that the healthy hemisphere can play a role in the recovery of stroke in the subset of patients who have experienced improved recovery. Perhaps the stimulation protocols should also take account of this population of patients.

In practicum, it is important to be able to translate these effects and principles of inter-hemispheric interaction to the generalized stroke population. Specifically, this analysis raises the point of how stimulation should be altered in the setting of bilateral strokes. In this patient population, would the same alteration of inter-hemispheric balance still be applicable? If so, does one select the side to inhibit or facilitate based on the severity of the contralateral side? Would the improvement in one side be at the expense of the other side's motor or cognitive effects? What excitability relationship does the new and the previous lesion have with one another in the balance of inter-hemispheric interaction? How do we propose to balance their effects? These questions are not only applicable in the understanding of the inter-hemispheric interaction, but also its application. It becomes especially tangible given the high risk of yearly recurrence of stroke of 185,000 in the United States alone. The scenario of multiple strokes is significantly common. Ergo, this topic would benefit from further consideration in the design and optimization of this intervention.

The concept of intra-cortical facilitation should also be further optimized. As has been previously demonstrated, the activity of the peri-lesional region can be increased with non-invasive stimulation (Takeuchi et al., 2009). However, attempts should further be made to delineate the localization of application. How does one definitely determine the ideal location? Should it be by fMRI, EEG, or optimal scalp position (OSP)? If so, how does one compensate with tDCS paradigms, given there is a difference between the electrode placement and the exact location where the current is flowing. In order to direct treatment, one would have to provide accurate parameters and titration guidelines in order to provide prescriptions that will effectuate improvement in care.

It is undetermined if the stroke recovery to the primary motor cortex has a specific role in improvement of dexterity (Rouiller et al., 1998). In certain articles, there is an improvement in dexterity without improvement in force. In these cases, is the improvement in dexterity due to a particular predilection for dexterity in the motor cortex? Alternatively, is there a relative higher difficulty in improvement of force generation in the lesioned patient? (Sohn et al., 2002; Liepert et al., 2007). Elucidation of this aspect will also help to individualize stimulation parameters and select motor assessment outcomes.

SHAM: UTILIZATION OF PLACEBO STIMULATION

Given the earlier discussion on the unknown optimal protocol for stimulation, one may question whether one is inducing motor changes in the 90° and vertex sham stimulation methods. This might be even more applicable in patients with stroke who have or are currently undergoing neuroplasticity of cortical pathways. It is unclear if there are effects on these new or old motor pathways in producing an alteration in motor outcome. One would need to determine how well these procedures mimic active (or real) stimulation without producing confounding changes in order to provide a more ideal unblemished placebo comparison.

The issue of placebo is an aspect that will need to be addressed in future studies. As mentioned above, not all the articles included in our review used a placebo group to compare against the intervention groups. There was also a significant amount of heterogeneity in the type of placebo. Therefore, a standardized sham stimulation protocol must be initiated in order to rule out placebo effects out in non-invasive brain stimulation intervention studies. This is especially important in the context that motivation to perform an activity may be associated with a noticeable placebo effect. Considering that these therapies involve constant contact with researchers or therapists, it may present some positive effects over the patients' rehabilitative drive and motor effort. Because these studies did not sufficiently sham or mask treatment, it is possible that the results found were due to a placebo effect. However, since there were also improved measures of cortical excitability, it is less likely the improvements observed were related to increased effort alone. Nevertheless, randomized sham-controlled trials that explore non-invasive stimulation would have to be a standard in the future development of non-invasive brain stimulation studies in the stroke population.

MOTOR ASSESSMENT TOOLS AND EFFECTS: STRENGTH VERSUS DEXTERITY

Given the numerous different assessment tools that were utilized for the neurostimulation articles, we simplified them into **Table 2**. They varied in the types of assessment tools and their times of implementation. These assessment tools have the ability to study different aspects of motor function and impairment. This point of cogitation generates a discussion whether an outcome is an optimal assessment. Given the broad concept of motor ability, each motor movement is comprised of multiple different sub-abilities that involve various parts of the brain and neurological system. We contemplated the optimal state of the measures being studied whether one is studying clinical, research, or surrogate outcomes. An Australian study explores this point in stroke survivors by noting that inclusion of consumers to gage and rank personal significance and implications of motor outcomes can be helpful in research priority setting (Sangvatanakul et al., 2010). Park et al. (2008) establishes that baseline clinical

measurements and research motor assessments can be used to predict clinically meaningful outcomes in patients with stroke (Park et al., 2008). This may be an interesting colloquy in the future, as the determination of improvement is translated to the clinical arena.

We explore the concept of motor implications in our discussion of strength versus dexterity. In the selected articles, there were articles that did not show increase in strength, but showed increased dexterity instead (Liepert et al., 2007). This phenomenon of dissociation of strength and dexterity is well described by Noskin et al. (2008), who studied 30 patients with first time unilateral strokes. They hypothesized that the ipsilateral hand could be proven to be functionally impaired from the initial 24–48 h of the stroke and up to 1 year of follow-up (Noskin et al., 2008). They successfully predicted that the impairments of dexterity and strength would diverge both in the acute phase and in the recovery process, with the aim of proving independent modes of malfunction (Noskin et al., 2008). As further evidence, the impairments in dexterity maintained correlations with one another despite the lack of correlation between dexterity and stroke impairments (Noskin et al., 2008).

This raises the following questions: (1) whether it is easier to provide improvement in dexterity versus strength; (2) whether it requires more neuronal improvement/preservation to generate more force than dexterity; and (3) whether dexterity improves based on recruitment of additional neuronal tracts versus recovery of the original impaired neurons. Noskin et al., 2008 suggests that the various aspects of motor function require multifarious degrees of bilateral cortical involvement and input (Noskin et al., 2008). This is supported by fMRI data that demonstrate that various complex motor tasks require bihemispheric activity, especially for motor planning, sequencing, and integration of sensorimotor information (Haslinger et al., 2002; Filippi et al., 2004; Krakauer, 2005; Poldrack et al., 2005). Furthermore, TMS data has proffered accepted elucidations of ipsilateral impairments through the concept of inter-hemispheric interactions via transcallosal connections (Haaland and Delaney, 1981; Haaland and Harrington, 1989; Shimizu et al., 2002). This hints that the concept of dexterity is a multi-faceted sub-component of motor function that likely differing effects and outcomes from the stroke. The literature also suggests that the post-stroke motor network is influenced by other neuronal phenomena such as deafferentation, and circuit connections with the basal ganglia and cerebellum (Parent and Hazrati, 1995; Schmahmann and Pandya, 1997). A simpler question is whether it is more difficult to modify force generation (Rouiller et al., 1998; Sohn et al., 2002; Liepert et al., 2007)? Recent literature demonstrates that it is possible to apply non-invasive stimulation (cathodal tDCS) to the cerebellum to invoke motor adaptive learning improvement (Galea et al., 2011). We question if the dissociation between strength versus dexterity improvement would be further elucidated with stimulation was applied to the cerebellum instead of the motor cortex. These studies adumbrate the point of the variability of outcome assessments used in the articles. It is capital that future studies design specifically for strength and dexterity outcomes and localize these changes to the motor cortex or the respective involved loci. The application of the above aspects and sub-classification of motor function would be informative and essential for future studies to evaluate the comparisons of learning and improvement in neuroplasticity.

LONG-TERM

As described above, there is a subset of the selected articles that performed long-term follow-up. The time-periods varied from 30 min (Takeuchi et al., 2005) to 1 year (Khedr et al., 2010). A distinctive observation of the Khedr et al. (2010) article is the prolonged duration of preserved effects. An aspect that makes it to be particularly informative is that the stimulation was implemented in the acute phase of the stroke. This highlights the earlier discussion on the ideal window of time for intervention, whether it is beneficial to intervene early or later in the course. Due to this study, we contemplate if chronic stroke cases would show further improvement if follow-up was provided greater than 1 year. Another notable observation was regarding the type of assessment used for follow-up. It is worthy of discussion that the Fugl-Meyer score did not reveal an improvement immediately post-rTMS stimulation in another study but showed a difference 1 week later (Yozbatiran et al., 2009). It may that the long-term improvements that occur after stimulation are due to long-term potentiating effects and therefore manifest slowly and gradually over time. This might explain the trend of delayed improvement noted in the Fugl-Meyer (Yozbatiran et al., 2009).

LIMITATIONS

There are some limitations related principally to the information content in the selected article. Some articles did not provide necessary information to calculate the effect size, besides they did not give enough demographic information of the patient and better description of side effect.

RECRUITMENT

One problem with study recruitment is that it is that novel therapies are typically only available in academic areas. Thereby, the study groups would be primarily comprised of patients who reside in proximity to these areas. This may limit the generalizability of results in non-academic populations. Moreover, these patients may have differing access to acute stroke management, given the narrow window of antithrombotic treatment. This may also affect the generalizability to rural and lower-access regions. It may be interesting in the future to appraise how increases in the availability of these therapies affect the epidemiological outcome and translational applicability.

FUTURE DIRECTIONS

This review shows that there is a plethora of areas that need to be studied in the field of neuromodulation to optimize the analysis of motor recovery of stroke patients. Although many of the future suggestions were listed above, we summarize some of them here. In essence, future directions would lead toward the standardization of investigation and application. Specifically, future studies will have to evaluate motor assessments and elucidate which would be the most prudent and applicable choice. We will have to further evaluate safety parameters of stroke patients, especially as we explore the future use of high-frequency rTMS. Future studies should help develop homogeneity in sham procedures as

well. Most importantly, it would be helpful to ascertain motor assessment data that are attuned to specific stroke baseline characteristics (age, stroke duration, and stroke location), which would facilitate individualization and optimization of treatment.

CONCLUSION

From this analysis of collected studies (**Tables 1–4**), it is observable from the available data that non-invasive stimulation may beneficial in enhancing motor recovery. Specifically, it may lead to clinically meaningful functional motor improvements in the stroke population. Future studies would benefit from future standardization of outcomes and stimulation parameters in order to decrease variability and heterogeneity of results. Future studies should also help delineate the subtypes of patients that do not benefit from specific parameters. These changes would be helpful in understanding how to individualize therapy to various stroke sub-populations, with the aim of the optimization of neurorecovery of motor function.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Neuropsychiatric_Imaging_and_Stimulation/10.3389/fpsyt.2012.00088/abstract

Table S1 | Adverse events and safety outcome for selected peer-reviewed articles. MMSE, mini-mental state examination; EEG, electroencephalography.

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Finite-element model predicts current density distribution for clinical applications of tDCS and tACS

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Transcranial direct current stimulation (tDCS) has been applied in numerous scientific studies over the past decade. However, the possibility to apply tDCS in therapy of neuropsychiatric disorders is still debated. While transcranial magnetic stimulation (TMS) has been approved for treatment of major depression in the United States by the Food and Drug Administration (FDA), tDCS is not as widely accepted. One of the criticisms against tDCS is the lack of spatial specificity. Focality is limited by the electrode size (35 cm^2 are commonly used) and the bipolar arrangement. However, a current flow through the head directly from anode to cathode is an outdated view. Finite-element (FE) models have recently been used to predict the exact current flow during tDCS. These simulations have demonstrated that the current flow depends on tissue shape and conductivity. To face the challenge to predict the location, magnitude, and direction of the current flow induced by tDCS and transcranial alternating current stimulation (tACS), we used a refined realistic FE modeling approach. With respect to the literature on clinical tDCS and tACS, we analyzed two common setups for the location of the stimulation electrodes which target the frontal lobe and the occipital lobe, respectively. We compared lateral and medial electrode configuration with regard to their usability. We were able to demonstrate that the lateral configurations yielded more focused stimulation areas as well as higher current intensities in the target areas. The high resolution of our simulation allows one to combine the modeled current flow with the knowledge of neuronal orientation to predict the consequences of tDCS and tACS. Our results not only offer a basis for a deeper understanding of the stimulation sites currently in use for clinical applications but also offer a better interpretation of observed effects.

Keywords: tDCS, tACS, finite-element modeling

INTRODUCTION

In the past years, non-invasive brain stimulation techniques have gained interest in the treatment of psychiatric and neurological disorders. Especially repetitive TMS (rTMS) and transcranial electrical stimulation (TES), which comprises tDCS as well as tACS, have proven to be successful candidates as tools for therapeutic treatment. However, while TMS has been approved for treatment of major depression by the FDA, the promising results of tDCS-studies on the treatment of neurological and psychiatric diseases have not be put into everyday practice (George and Aston-Jones, 2010). Numerous studies have shown that tDCS is feasible for a wide range of disorders, e.g., motor disorders after stroke (Hummel et al., 2005; Edwards et al., 2009), post stroke aphasia (Monti et al., 2008; Baker et al., 2010), epilepsy (Fregni et al., 2006b; Nitsche and Paulus, 2009), chronic pain (Boggio et al., 2009), Parkinson's disease (Boggio et al., 2006; Benninger et al., 2010), and Alzheimer's disease (Ferrucci et al., 2008; Boggio et al., 2011). Furthermore, tDCS has demonstrated its potential to modulate working memory performance which could be used to treat neuropsychiatric deficits (Zaehle et al., 2011; Heimrath et al., 2012). Appealing characteristics of TES comprise cost, usability, and sham-control. TES devices are affordable, compared to TMS, weigh less than 1 kg and can easily be used at home or as a mobile device. Additionally, tDCS can easily be sham-controlled and has mostly well-tolerated, mild adverse effects.

Because some neurological and psychiatric disorders involve altered brain activity, the potential of tDCS to modulate this activity is obvious. Electrical stimulation is a candidate to facilitate impaired function or to suppress maladaptive plasticity (Paulus, 2011). TDCS uses a direct current with low intensity which is passed into the brain via scalp electrodes. Spontaneous neural activity is modulated in a polarity dependent manner (Bindman et al., 1964; Nitsche and Paulus, 2009). Anodal tDCS leads to a depolarization of the resting membrane potential and enhances cortical excitability whereas cathodal tDCS leads to a hyperpolarization and a reduction of cortical excitability. These effects can outlast the stimulation for an hour or even longer, given sufficient duration of stimulation (Nitsche and Paulus, 2000, 2001). Other electrical stimulation techniques use oscillating currents (Marshall et al., 2006; Antal et al., 2008; Kanai et al., 2008; Zaehle et al., 2010). TACS and tACS with an offset called oscillating transcranial direct current stimulation (otDCS) are able to

modulate the ongoing rhythmic brain activity and could be used to treat diseases that are associated with disturbed brain oscillations (Herrmann and Demiralp, 2005; Uhlhaas et al., 2008). It can be concluded, that tDCS and tACS offer a wide range of possible therapeutic application and their potential has already been demonstrated in numerous pilot studies. Two of the major target areas of these studies were the visual cortex and the frontal cortex.

Targeting the visual cortex with tDCS and tACS could be beneficial for diseases with deficient visual processing and changes in excitability of visual areas (e.g., amblyopia, migraine, and neglect; Antal et al., 2004). Halko et al. (2011) demonstrated with a case study that tDCS facilitated rehabilitation of hemianopia. Additionally, Sabel et al. (2011) have successfully applied peripheral ACS to the visual system in the restoration of visual function in patients with optic neuropathy. They also reported long lasting EEG changes in the occipital cortex after stimulation. Furthermore, studies on healthy volunteers with tDCS (Antal et al., 2003; Antal and Paulus, 2008; Chaieb et al., 2008) and tACS (Kanai et al., 2008; Zaehle et al., 2010) have proven their capability to modulate excitability of the visual cortex.

The frontal cortex has been stimulated to manipulate excitability in different areas. For example, anodal stimulation aiming at the left frontal gyrus, which is essential for speech production (Hillis et al., 2004), facilitated this function (Baker et al., 2010; Fridriksson et al., 2011; Holland et al., 2011; Marangolo et al., 2011). The authors argued that this design could be used to treat aphasic stroke patients. In major depression, pathologically altered activity of the prefrontal cortex has been demonstrated. Compared to the right dorsolateral prefrontal cortex (dlPFC), the left dlPFC is hypoactivated (Grimm et al., 2008). A bilateral frontal application of the tDCS electrodes would therefore be very convenient to achieve a balance of left and right dlPFC, i.e., excitability enhancement of the left dlPFC and an excitability reduction of the right dlPFC. Studies on the antidepressive effect of prefrontal tDCS provided promising results (see Nitsche and Paulus, 2009 for a review; Kalu et al., 2012 for a meta-analysis). Major advantage of tDCS in depression therapy might be its immediate effect compared to the delayed effect of depression pharmacotherapy (Rigonatti et al., 2008) and its benefits for patients who do not respond to pharmaceutical interventions (Dell'Osso et al., 2011).

An important aspect of the mechanisms of TES is the magnitude and location of the induced current. Although tDCS is rather non-focal, the locations of the stimulation electrodes are critical for the amount of current being shunted through the scalp, how much is delivered to the brain, and to what regions (Miranda et al., 2006; Feira et al., 2009). In clinical contexts, it is crucial to know if the electrode positions are suited to induce an electric field in the target brain area and furthermore, if the induced current is of sufficient magnitude. A further critical aspect of tDCS is the direction of the current flow with regard to the neuronal orientation in space (Nitsche and Paulus, 2000). To address these issues, we used a realistic finite-element modeling approach on lateral and medial electrode configurations targeting the occipital or frontal cortex. Our results allow for high resolution insights into the current flow in the targeted brain areas and are discussed with respect to their usability.

MATERIALS AND METHODS

tDCS SIMULATION

For a tDCS simulation study, a realistic FE model of the head was generated from a T1-weighted, a T2-weighted and a diffusion-tensor (DT)-magnetic resonance image (MRI) of a healthy 26-year-old male subject. In a first step, the T2-MRI was rigidly registered onto the T1-MRI using a mutual information based cost-function (Jenkinson and Smith, 2001). Segmentation into tissue compartments skin, skull compacta, skull spongiosa, cerebrospinal fluid (CSF), brain gray (GM), and white matter (WM) was then performed using the FSL software[1] (Zhang et al., 2001; Smith, 2002; Jenkinson et al., 2005). Segmentation started with the generation of initial masks for skin, inner and outer skull, and brain using both T1- and T2-MRI. In a second step, the T1-MRI served for GM and WM segmentation, while the T2-MRI allowed for a segmentation of skull compacta, skull spongiosa, and CSF space (see **Figure 1**). For the compartments of skin, skull compacta, skull spongiosa, and CSF, we used the isotropic conductivity values of 0.43, 0.007, 0.025, and 1.79 S/m, respectively (Baumann et al., 1997; Akhtari et al., 2002; Dannhauer et al., 2011). For the modeling of white matter conductivity anisotropy, the diffusion-weighted images were first artifact-corrected using our reversed-gradient approach introduced in Olesch et al. (2010). Diffusion tensors were then determined and the result was registered onto the structural images using the FSL routine vecreg[2]. In a last step, the conductivity anisotropy in GM and WM was computed from the registered DTI using an effective medium approach (Tuch et al., 2001; Rullmann et al., 2009). This resulted in mean conductivities of 0.19 and 0.24 S/m for WM and GM.

Two electrode patches with a size of 7 cm × 5 cm, thickness of 4 mm, and saline like conductivity of 1.4 S/m are modeled. A total current of 1 mA is injected at the red patch (anode) and removed at the blue one (cathode). For field modeling of this stimulation throughout the volume conductor, a quasistatic approximation of Maxwell's equations (Plonsey and Heppner, 1967) was used, resulting in a Laplace equation for the electric potential Φ with inhomogeneous Neumann boundary conditions at the head surface. An isoparametric FE approach is used for the computation of Φ in a 1 mm geometry-adapted hexahedral mesh (Wolters et al., 2007a,b), resulting in a large sparse linear equation system with 2.255 million unknowns, which is solved using an algebraic multigrid preconditioned conjugate gradient approach (Wolters et al., 2002; Lew et al., 2009). In a last step, the current density $J = \sigma$ grad Φ is computed with σ being the 3×3 conductivity tensor. For simulation, we used our software SimBio[3].

In all subsequent figures, slices of the current density distribution through the cortex are presented. The amplitude of J is coded by means of a linear color-scale. The current density distributions were computed in the 1 mm geometry-adapted hexahedral head model and the software SciRun[4] was used for visualization.

[1] http://www.fmrib.ox.ac.uk/fsl
[2] http://fsl.fmrib.ox.ac.uk/fsl/fdt/fdt_utils.html#vecreg
[3] http://www.mrt.uni-jena.de
[4] http://www.sci.utah.edu/cibc/software/106-scirun.html

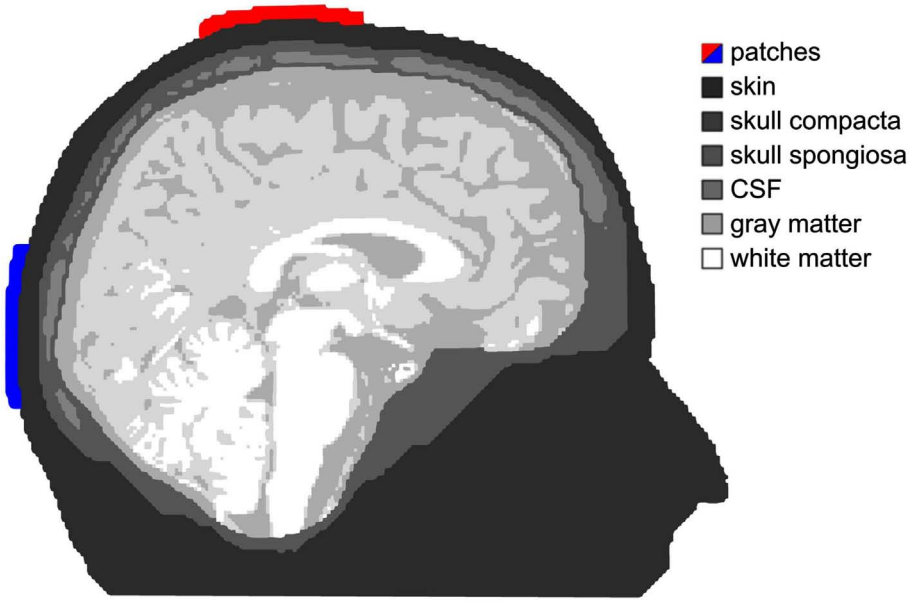

FIGURE 1 | Tissue compartments. Shades of gray depict the different tissue compartments used in our simulation. The anode is colored red and the cathode is blue. This applies for all simulation figures.

RESULTS

GENERAL FINDINGS

The strongest current flow was observed within the skin (peak current density 1.7 A/m^2), since the conductivity of skin is much better than that of bone. For this reason, current densities in skin were not visualized. Otherwise, the pattern of the intracranial currents could not be made visible. Inside the skull, conductivity of cerebrospinal fluid is again much better than that of GM and WM. Thus, also current densities within CSF (peak current density 0.378 A/m^2) are not visualized.

A general phenomenon that could be observed for the current densities in GM and WM was the fact that cerebral regions adjacent to CSF showed stronger current densities than more remote areas. Gyri and small structures that protrude into CSF receive strongest current densities. Current densities within gray and white matter were in the range of 0–0.1 A/m^2.

ELECTRODE MONTAGE FPz/Oz

Figure 2 depicts the current densities when stimulation electrodes are centered around 10–20-electrode positions FPz and Oz. As can be seen from the figure, current flow is rather widespread and reaches all cortical lobes. The montage is not ideal for a selective stimulation of the frontal lobe. Occipital cortex receives stronger currents than frontal cortex – albeit mainly in gyri adjacent to the interhemispheric cleft as current density is generally strong in those areas of GM that lie close to CSF.

ELECTRODE MONTAGE F7/F8

Figure 3 displays the pattern of current densities for the electrodes being centered around 10–20-electrode positions F7 and F8. Current flow is not restricted to but focused to frontal regions. Temporal and parietal cortex receive significantly weaker stimulation and occipital cortex almost none. This montage is, therefore, well suited to stimulate frontal brain areas without too much involvement of other cortical lobes.

ELECTRODE MONTAGE Cz/Oz

Figure 4 depicts the pattern of current densities when stimulation electrodes are centered around 10–20-electrode positions Cz and Oz. Parietal and occipital cortex show strong current densities in the range of 0.05–0.15 A/m^2. Frontal brain regions receive significantly less stimulation current with the exception of the orbito-frontal cortex. The montage seems well suited for occipital stimulation. Note, however, that current density is stronger in medial than in lateral occipital cortex.

ELECTRODE MONTAGE P7/P8

Figure 5 displays the current densities for electrodes being centered around 10–20 locations P7 and P8. Posterior brain areas receive strongest stimulation (up to 0.089 A/m^2). However, also parietal and temporal cortex reach current densities in the range of 0.03–0.07 A/m^2. Even some gyri of the frontal lobe that are close to CSF receive current densities up to 0.05 A/m^2. The electrode montage is suited to stimulate occipital cortex. In contrast to the Cz/Oz montage, the current flow elicited by the P7/P8 montage is not limited to medial parts of the occipital cortex but reaches also the more lateral regions.

DISCUSSION

USABILITY FOR OCCIPITAL STIMULATION

As our simulation has demonstrated both, Cz/Oz and P7/P8 electrode montage are suited for stimulating the occipital cortex. This

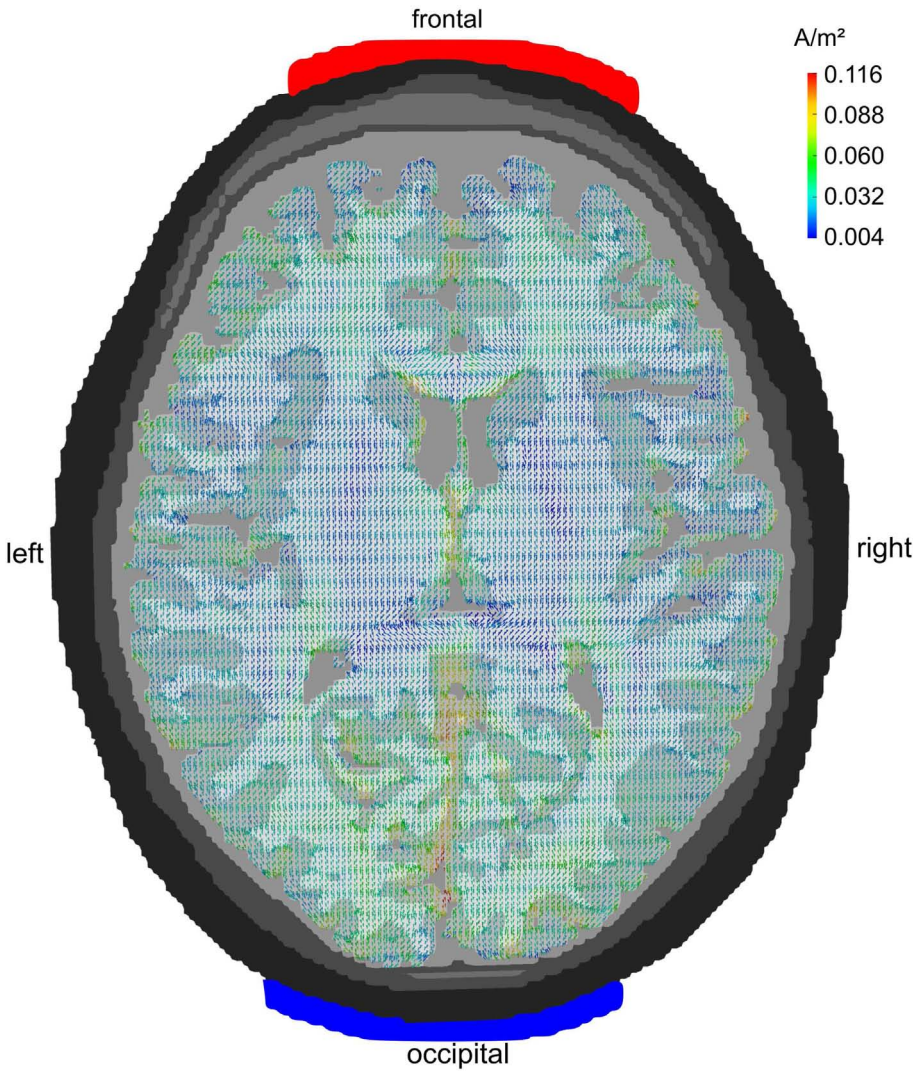

FIGURE 2 | Midline configuration FPz/Oz: axial view. Stimulation electrodes are centered around electrode positions FPz and Oz. The current density is not very focal but rather widespread. All cortical lobes show current densities above 0.07 A/m^2. The maximum current flow is in the occipital cortex.

confirms the results of existing studies. Usually a Cz/Oz montage is used for tDCS (see Antal et al., 2008 for an overview) as well as for tACS (Kanai et al., 2008). But especially for tACS the problem of retinal phosphenes arises (Paulus, 2010). The closer one of the stimulation electrodes is to the eyes, the easier phosphenes are perceived. This especially holds true for the FPz/Oz configuration, an effect that our simulation confirms. An alternative would be the P7/P8 configuration which is far away from the eye balls and was successfully used with tACS by Zaehle et al. (2010). They adjusted the stimulation strength individually to assure that no phosphenes were elicited by the stimulation. Nevertheless, our simulation reveals that even with this montage, frontal areas might receive moderate electrical input. This makes it mandatory to stimulate the visual cortex below the individual phosphene threshold in order to avoid stimulation of the retina.

When applying tACS, modeling current flow reveals two different modes of stimulation. When two stimulation electrodes are placed at homologous location in the two hemispheres (e.g., P7/P8), this results in the two hemispheres being stimulated at 180˚ phase shift. Typically, brain oscillations are generated by two symmetrically located neural generators – one in each hemisphere (Chapman et al., 1984; Rodin and Rodin, 1995). Furthermore, two homologous electrodes in the two hemispheres usually oscillate without significant phase shift (Nikouline et al., 2001; Nunez et al., 2001). Since interhemispheric phase synchronization reflects functional coupling (Varela et al., 2001), cognitive functions that require the two oscillators to operate without phase shift could be disturbed by such an out of phase stimulation. Another type of stimulation would be achieved with electrodes being arranged along the midline (e.g., Cz/Oz). Here, the two lateral generators of an oscillation would be stimulated without phase shift.

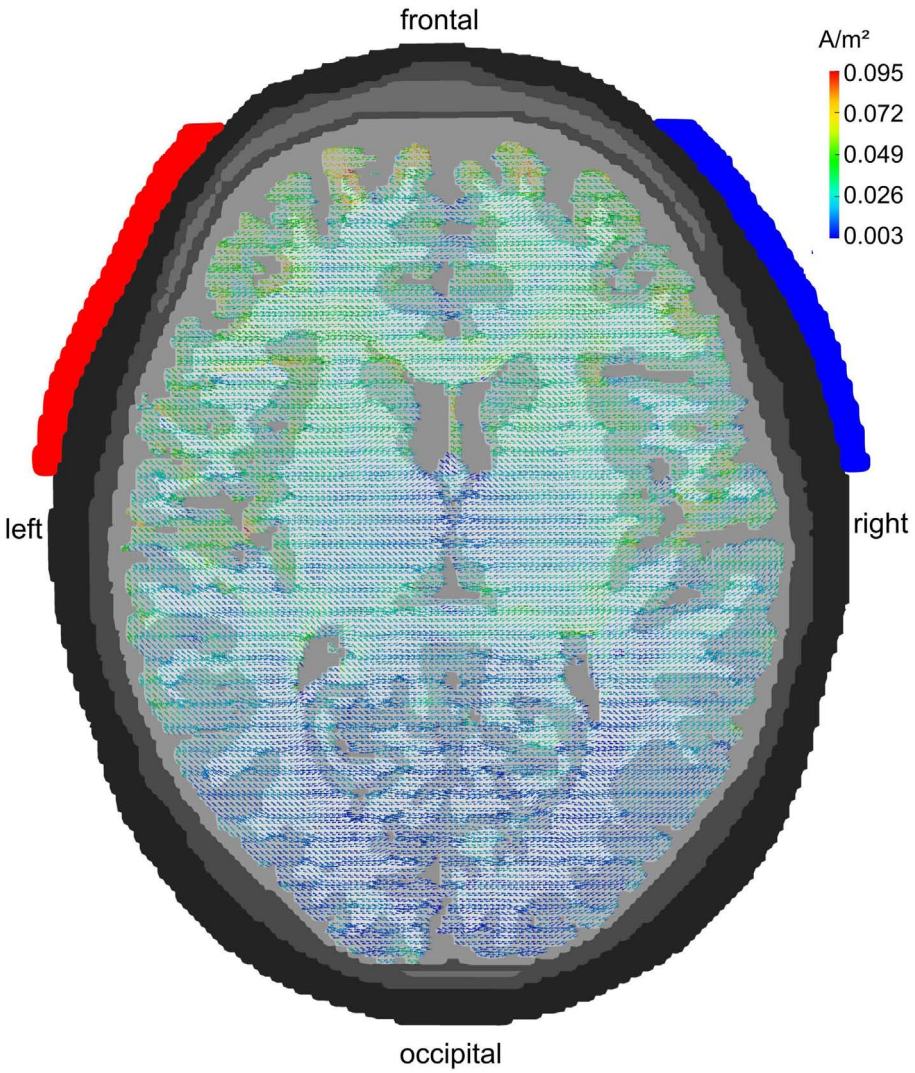

FIGURE 3 | Lateral configuration F7/F8: axial view. Stimulation electrodes are centered around electrode positions F7 and F8. The current density is clearly localized to the frontal cortex. Temporal and parietal lobes show only weak current densities and the occipital lobe receives hardly any stimulation.

USABILITY FOR FRONTAL STIMULATION

Our simulation clearly demonstrated that a midline configuration (FPz/Oz) is not suited to stimulate the frontal lobe. Due to the CSF in the interhemispheric cleft, current flow is rather non-focal. Therefore, a bilateral configuration (F7/F8) is advantageous. Firstly, a strong current flow in the frontal lobe is apparent and, secondly, the current flow is rather focal and other cortical areas receive no or weak current densities. Thirdly, current strength on both hemispheres is similar which makes a bilateral configuration especially suitable for the application in depression therapy. While some studies used a configuration with the anode over the left frontal lobe and the cathode over the right orbit (e.g., Fregni et al., 2006a; Boggio et al., 2008), a symmetrical configuration might be better suited. This way, the excitability of the left dlPFC could be enhanced and, simultaneously, the excitability of the right dlPFC could be reduced. Thus, tDCS could be more effective and at the same time lower stimulation intensities might be required to obtain the deserved effects. Another obvious aspect of our simulation is that within the frontal lobe the activation is rather widespread. Even if the dlPFC is the target of the stimulation it is difficult to argue that the observed effects are elicited by a selective modulation of the activity of the dlPFC. The same argument holds true for the stimulation of Broca's area. Marangolo et al. (2011) stimulated three aphasic patients with brain lesions to different cortical structures functionally connected to Broca's area. Although the same electrode configuration was used, all subjects exhibited improvement in speech production.

GENERAL DISCUSSION

The analysis of the current densities in our realistically shaped finite-element model revealed the strongest current flow to be in the skin of the scalp. This effect is due to the better conductivity of skin as compared to bone and has been described previously for spherical (Miranda et al., 2006) and realistic head models

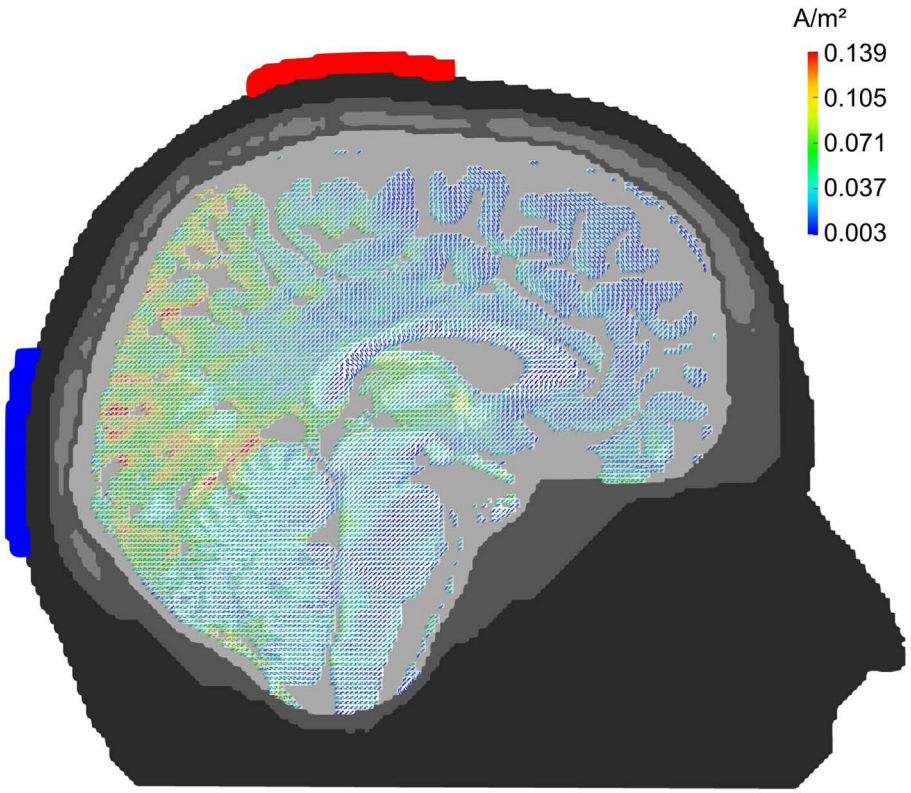

FIGURE 4 | Midline configuration Cz/Oz: sagittal view. Stimulation electrodes are centered around electrode positions Cz and Oz. The pattern of current densities shows a clear maximum in posterior brain areas, especially in occipital cortex.

(Salvador et al., 2010). In fact, the strong current density of more than 1 A/m^2 is about 10 times stronger than that in brain tissue. Therefore, we had to disable the visualization of current flow in the scalp in order to see more subtle patterns of current densities inside the skull. Along the same lines, within the skull current densities in CSF were much stronger than in brain tissue. This effect is also due to the better conductivity of CSF as compared to gray or white matter and has been described before for realistic head models (Salvador et al., 2010). A further phenomenon was the pattern of current densities within gray and white matter. Generally speaking, current density was always stronger in tissue adjacent to CSF. Especially, gray matter structures (e.g., gyri) peaking into CSF resulted in strong current densities. CSF "shunts" the current flow so that nearby structures exhibit stronger current flow. This indicates that individual anatomical differences can have an effect of the current flow during TES. Thus, ideally one would want to compute individual head models to simulate the current flow for the individual patient to be stimulated (Halko et al., 2011). With this procedure, one could adjust the electrode positions and avoid inadequate stimulation sites. However, this requires MRI images of each patient and is computationally expensive and time consuming. Nevertheless, software solutions like the free SimNIBS (Windhoff et al., 2011) are already available.

In addition to tDCS, also tACS has recently been applied in therapy of neurological patients (Sabel et al., 2011). The idea of tACS is to interfere with brain oscillations which are known to be relevant for human cognition (Herrmann et al., 2004) and to be disturbed in some psychiatric and neurologic diseases (Herrmann and Demiralp, 2005; Uhlhaas et al., 2008). TACS is capable of enhancing the amplitude of ongoing brain oscillations (Zaehle et al., 2010). In our model, current flow was always from the anode to the cathode as can be seen from the direction of the cones that represent the direction of current flow. If anode and cathode are interchanged, this yields the same pattern of current densities. However, the direction of each cone of current flow flips by 180° (Wagner et al., 2007). For tACS, the direction of current flow flips back and forth for every half-wave of the stimulation (**Figure 6**).

Additionally, one has to take into account other possible electrode montages. Different electrode sizes (Nitsche et al., 2007), shapes (Datta et al., 2008, 2009), and number of electrodes (Feira et al., 2009) can help to overcome the limitation of the focality of TES. The simulation with modeling studies will help to make predictions about the outcome of a specific electrode montage with specific stimulation-parameters on a specific individual. Therefore, experiments have to follow to take the predictions into practice and eventually into therapy.

Our results raise the question whether weak currents applied with TES are able to influence the activity of cortical neurons in the human brain. In our modeling study we demonstrated that TES can lead to significant current flow inside the human

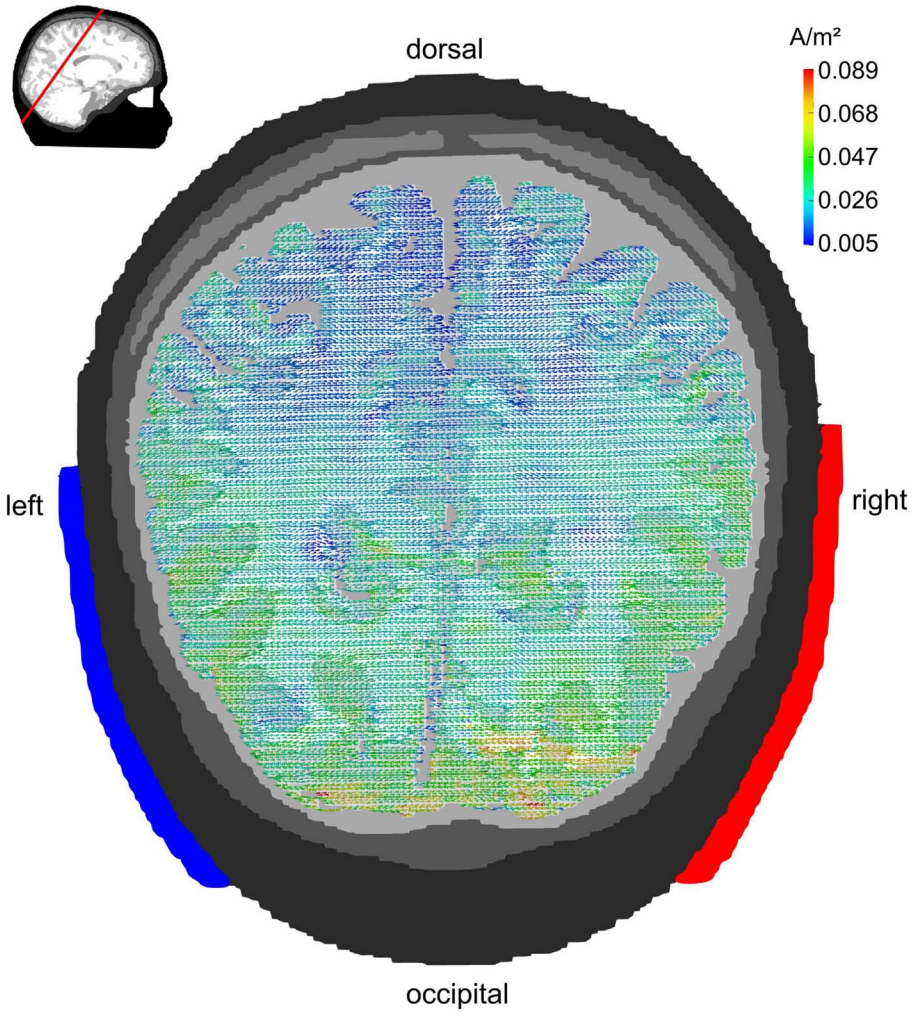

FIGURE 5 | Lateral configuration P7/P8: transversal view. Stimulation electrodes are centered around electrode positions P7 and P8. The pattern of current densities shows a clear maximum over posterior brain regions. However, the current flow is not restricted to occipital cortex but reaches also parietal and temporal cortex. The embedded figure in the upper left corner depicts the section slice.

cortex, despite a large amount of the current being short-circuited by the well-conducting skin (Holdefer et al., 2006). Intracranial electric stimulation of neurons in animals has demonstrated that axons and especially the axon hillock are sensitive to this kind of stimulation due to the high number of voltage-sensitive Na ion channels (Nowak and Bullier, 1998). Francis et al. (2003) were able to demonstrate that electric fields of 140 μV/mm are sufficient to increase the firing rate of single neurons (i.e., super-threshold stimulation). Miranda et al. (2006) used an isotropic spherical head model to demonstrate that 2.0 mA of tDCS results in 0.1 A/m^2 corresponding to an electric field of 220 μV/mm. Our anisotropic simulation revealed current densities in the GM up to 0.1 A/m^2. Dividing that value by the GM conductivity of 0.24 S/m reveals electric fields up to 417 μV/mm, which can be considered super-threshold. Additionally, one has to keep in mind that the current densities in the GM depend linearly on the total current. When the total current is doubled, the current densities in the GM will be 0.2 A/m^2. Miranda et al. (2006) used a total current of 2.0 mA which is twice of what we used in our study. However, they used a significantly higher skin to skull conductivity ratio (75:1, while we used 43:1). Thus, major currents were short-circuited by the skin and minor currents penetrated the low conductive skull. Therefore, the current densities in the GM in both studies are comparable.

Modeling studies have elaborated on the effects of the size and position of the "return" electrode (Datta et al., 2010). They demonstrated that both parameters have a strong influence on the specificity of the stimulation and the current flow under the "stimulating" electrode. Furthermore, electrode locations are critical with regard to the amount of current shunted through the scalp (Miranda et al., 2006). Modeling studies can provide valuable insights about the general effects of the positions of the electrodes.

One has to keep in mind that simplified rules (e.g., anode – enhanced excitability, cathode – reduced excitability) can be misleading, because the distribution of the current flow through

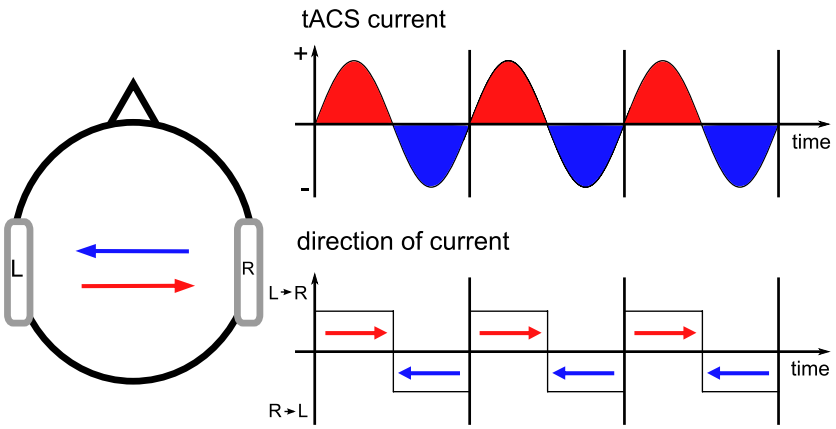

FIGURE 6 | Current flow during tACS. When current is applied sinusoidally, the direction of current flow flips back and forth by 180° for every half-wave. Let us consider the left stimulation electrode. During the positive half-wave, it represents the anode of a tDCS stimulation with variable amplitude. During the negative half-wave, the direction of current flow suddenly flips by 180°. During each half-wave the direction remains stable but the strength of the current flow varies. Stimulation electrodes are depicted in gray.

the head is much more complex. Common parameters of TES intensity (current intensity, duration of the stimulation, and overall electrode size) cannot predict the current that reaches the cortex. As other modeling studies demonstrated, the simulation of the current flow can help to define the correct tDCS intensity (Sadleir et al., 2010). A limitation of the usability of modeling approaches is represented by the parameters of the individuals, because cortical excitability is modulated by, for example, medication (Ziemann, 2003), which is especially relevant in clinical populations. This has to be considered when a study is conducted as it may affect the results.

Brunoni et al. (2012) concluded that the situation of TES is like the situation of TMS several years ago. A lot of studies have been conducted to explore the use of TES in therapy, but sample sizes were small and Phase III studies are still missing. We believe that modeling the current flow can help tDCS and tACS to reach therapeutic success in the future.

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Target optimization in transcranial direct current stimulation

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Transcranial direct current stimulation (tDCS) is an emerging neuromodulation therapy that has been experimentally determined to affect a wide range of behaviors and diseases ranging from motor, cognitive, and memory processes to depression and pain syndromes. The effects of tDCS may be inhibitory or excitatory, depending on the relative polarities of electrodes and their proximity to different brain structures. This distinction is believed to relate to the interaction of current flow with activation thresholds of different neural complexes. tDCS currents are typically applied via a single pair of large electrodes, with one (the active electrode) sited close to brain structures associated with targeted processes. To efficiently direct current toward the areas presumed related to these effects, we devised a method of steering current toward a selected area by reference to a 19-electrode montage applied to a high-resolution finite element model of the head. We used a non-linear optimization procedure to maximize mean current densities inside the left inferior frontal gyrus (IFG), while simultaneously restricting overall current, and median current densities within the accumbens. We found that a distributed current pattern could be found that would indeed direct current toward the IFG in this way, and compared it to other candidate 2-electrode configurations. Further, we found a combination of four anterior-posterior electrodes could direct current densities to the accumbens. We conclude that a similar method using multiple electrodes may be a useful means of directing current toward or away from specific brain regions and also of reducing tDCS side effects.

Keywords: tDCS, neuroplasticity, finite element model, optimization

INTRODUCTION

Transcranial direct current stimulation (tDCS) is an emerging method for modulation of brain function. Applications have been widely tested in experimental scenarios of motor, semantic, and attention processes (Nitsche et al., 2008). Other recent experimental uses include therapy for depression and hallucinations in schizophrenia (Brunelin et al., 2012; Loo et al., 2012).

The mechanism of tDCS is believed to arise through a modulation of baseline cortical excitability, caused by shifts in resting membrane potentials in regions experiencing current flow (Brunoni et al., 2012). The effects of tDCS depend on the relative polarity of electrodes. In general, anodal tDCS (where the active electrode is more positive than the reference electrode) has excitatory effects, and cathodal tDCS has inhibitory effects (Nitsche and Paulus, 2000). This has been substantiated in numerous experiments. For example studies of tDCS in cognitive tasks found that anodal tDCS delivered over the dorsolateral prefrontal cortex facilitated visual working memory (Fregni et al., 2005) and cathodal stimulation impaired short-term auditory memory performance (Elmer et al., 2009). Application of tDCS may, in turn affect the manifestations of neuropsychiatric conditions, including autism, depression, migraine, and schizophrenia, as baseline cortical excitability is characteristic of these conditions (Brunoni et al., 2012).

Little is known about the exact current flow patterns elicited by tDCS. Although methods using MRI scanners exist for measuring intracranial current flow (Scott et al., 1991), they are not conveniently applied because of the need for subject repositioning. Detailed models of current flow have therefore been created using finite element modeling in lieu of actual current measurement (Wagner et al., 2007; Datta et al., 2009; Sadleir et al., 2010). Though modeling is informative, there is still no clear mechanism linking current direction, current distribution, and observed experimental effects.

If it is possible to direct current toward or away from specific brain areas, the mechanisms, and structures responsible for the observed effects of tDCS may become clear. The ability to control current distribution throughout the brain may also provide a deeper understanding of general neural circuitry and networks. To best determine the stimulation parameters required to target different brain areas, we must refer to a complete electrical model of the head. This approach is natural because the paths

taken by transcranial currents are defined by head geometry and conductivity, as well as electrode shape and location.

In this study, we performed tests using a non-linear optimization technique to determine if current densities in brain structures could be shaped. We investigated three scenarios: one in which we wished to target cortical structures and to avoid the accumbens; a second in which we wished to target the region of the accumbens (left and right) with no constraint on regions to be avoided; and a third in which the accumbens was targeted, but the left inferior frontal gyrus (IFG) was avoided.

Other authors have used related optimization approaches (Im et al., 2008; Dmochowski et al., 2011; Park et al., 2011). While Im et al. (2008) used a evolution strategy approach to find optimal two-electrode locations from which to target a nominated brain area, a more recent work from their group used fixed anterior and posterior electrode location and a simplex algorithm to determine the appropriate current amplitudes needed to apply maximal currents (Park et al., 2011). Similarly, Dmochowski et al. (2011) used a fixed 64-electrode array and a variety of optimization approaches to determine current amplitudes needed to create maximal currents in a nominated cortical area.

Our methods use a general non-linear algorithm, which allows for flexible and general constraints to be applied. Dmochowski et al. (2011) used a similar approach. We used a linear basis for our computations comprising calculations of current flows between individual electrodes and a reference ground plane, whereas Park et al. (2011) and Dmochowski et al. (2011) used pairs of modeled electrodes to compute test intracranial current patterns. Our approach led to the *implicit* option to include extracranial electrodes. Normally the sum of all currents flowing into and out of the head should be zero. However, in part of the work presented here we have calculated optimal current flows through electrodes without this constraint. Any uncompensated current flowing through scalp electrodes after optimization can then be accounted for in real experiments by attaching an extracranial electrode to complete the circuit and supply the remaining current. As in Dmochowski et al. (2011) we used a general non-linear algorithm that allowed the inclusion of both target and avoidance areas. In contrast to their approach, we have explicitly specified avoidance areas rather than seeking to minimize current densities in all regions outside the target. Our method used large electrodes similar to those currently used in tDCS studies. Use of large electrodes avoids the risk of applying large currents to the skin, an effect that can lead to superficial burning. Finally, the model used as the base for our computations included white matter anisotropy. This more realistic model potentially facilitates better current localization and helped us discern an intriguing anatomical asymmetry in our test model.

MATERIALS AND METHODS

In the following sections we detail our electrical head model and the constructs and calculations used in optimization procedures.

TISSUE SEGMENTATION AND CONDUCTIVITY ASSIGNMENTS

We used the "Re-sliced Adam" (RA) dataset from the DTI White Matter atlas repository housed at the Johns Hopkins Medical Institutes (http://cmrm.med.jhmi.edu/). The RA model is a single subject atlas with a resolution of $1 \times 1 \times 1\,\text{mm}^3$ and includes white matter anisotropy vectors and T1 weighted (MPRAGE) MR images (Wakana et al., 2004). Segmentation was performed using both automatic classification and manual comparison with an anatomical atlas (Rubin and Safdieh, 2007). Non-brain data were segmented manually using ScanIP (Simpleware, Exeter, UK) software into 10 tissue types: cancelous bone, cortical bone, blood, cerebrospinal fluid (CSF), sclera, fat, muscle, brain, and skin. The original model did not include slices above the superior limit of the cortex. Therefore, to include the crown of the head, we extended the model by adding 12 slices (12 mm height) to the superior portion of the model, completing the head with CSF, cortical bone, and scalp materials. The brain tissue itself was further segmented automatically using FreeSurfer 5.0.0 (Cambridge, MA, USA) software into white matter and gray matter; and then subclassified into many cortical and deep brain structures. Specific target areas used in this study – the IFG, angular gyrus (AG), and dorsolateral prefrontal cortex (DLPFC) – were isolated using manually, referring anatomical atlas information.

Conductivity values were assigned to each tissue, chosen from measurements reported below 1 kHz. **Table 1** lists the sources for conductivities.

White matter was assumed anisotropic. We distinguished between conductivities of cancelous and cortical bone because of the large electrical property differences between these tissues (Akhtari et al., 2000, 2002; Sadleir and Argibay, 2007).

FINITE ELEMENT MODELING

The model solved the Laplace equation

$$\nabla \cdot \left(\sigma\left(x, y, z\right)\ \nabla\phi\right) = 0 \tag{1}$$

on the domain Ω (the head), subject to

$$\sigma\frac{\partial\phi}{d\mathbf{n}} = j \text{ and } \phi_{\text{base}} = 0; \tag{2}$$

Table 1 | Conductivities assigned to tissues in our model.

Compartment	Conductivity (S/m)	Reference
Air	0	–
Skin	4.3×10^{-1}	Holdefer et al. (2006)
Cerebrospinal fluid	1.8×10^{0}	Baumann et al. (1997)
Sclera	5.0×10^{-1}	Gabriel et al. (1996)
Cortical bone	5.52×10^{-3}	Akhtari et al. (2002)
Cancelous bone	21.4×10^{-3}	Akhtari et al. (2002)
Muscle*	1.6×10^{-1}	Geddes and Baker (1967)
Fat	2.5×10^{-2}	Gabriel et al. (1996)
Blood	6.7×10^{-1}	Geddes and Baker (1967)
White matter*	1.2×10^{-1} (trans.) 1.2×10^{-0} (long.)	Geddes and Baker (1967)
Gray matter	1.0×10^{-1}	Gabriel et al. (1996)

Values were chosen from available low frequency (<1 kHz) data in the literature. Compartments marked with an asterisk were anisotropic. The isotropic conductivity assigned to muscle was calculated according to the formula $\sigma^* = (\sigma_l\,\sigma_t)$ where σ_l is longitudinal and σ_t is transverse measured conductivity.

on the surface of the domain $d\Omega$. Here, $\sigma(x,y,z)$ is the conductivity distribution within the head, ϕ is the voltage distribution, j is the surface current density, and **n** is a vector normal to the surface. The quantity j was only non-zero on electrodes. The voltage on the base plane (the caudal slice) of the model (ϕ_{base}) was set to zero.

The segmented phantom was converted into a quadratic tetrahedral finite element model containing ∼18 million elements. In each white matter voxel, the anisotropic conductivity tensor was calculated as

$$\boldsymbol{D}_W = \boldsymbol{A}^T \boldsymbol{D}^*{}_W \boldsymbol{A}$$

where

$$\boldsymbol{D}^*{}_W = \begin{bmatrix} \sigma_l & 0 & 0 \\ 0 & \sigma_t & 0 \\ 0 & 0 & \sigma_t \end{bmatrix}$$ and $\boldsymbol{A} = \boldsymbol{R}_z\boldsymbol{R}_y\boldsymbol{R}_x$. $\boldsymbol{R}_z$, $\boldsymbol{R}_y$, and $\boldsymbol{R}_x$ are rotation matrices about the z, y, and x axes, respectively. In isotropic voxels, **D** was a diagonal matrix with all entries equal to the local isotropic conductivity value.

Computations of finite element model matrix equations and boundary conditions were implemented in C and solved using the preconditioned conjugate gradient method.

Electrode assignment and definition

Transcranial direct current stimulation current is normally introduced via a pair of large (∼35 cm^2) saline/sponge electrodes. One (the active electrode) is sited close to brain regions presumed involved in target processes. The other (the reference electrode) is placed elsewhere on the head or body. For this study, we defined a montage of NE = 19 electrodes (**Figure 1**). The electrodes were selected from standard 10–20 EEG locations. Each electrode had an area of ∼22 cm^2. Use of large electrodes reduces the risk that superficial burns will result from current application.

Boundary conditions

The base data used in the optimization procedure consisted of voltage data calculated between each electrode and a ground plane situated at the base of the model (**Figure 2**). In calculating the voltage data for each isolated electrode in turn, we simulated a total current of 1 mA injected into the head. Use of this single electrode arrangement allowed us to include the possibility that extracranial electrodes could be included (simply by allowing the sum of currents applied to the model to have a net non-zero value, implying that the extra current flowed through the neck and to an electrode located away from the head.

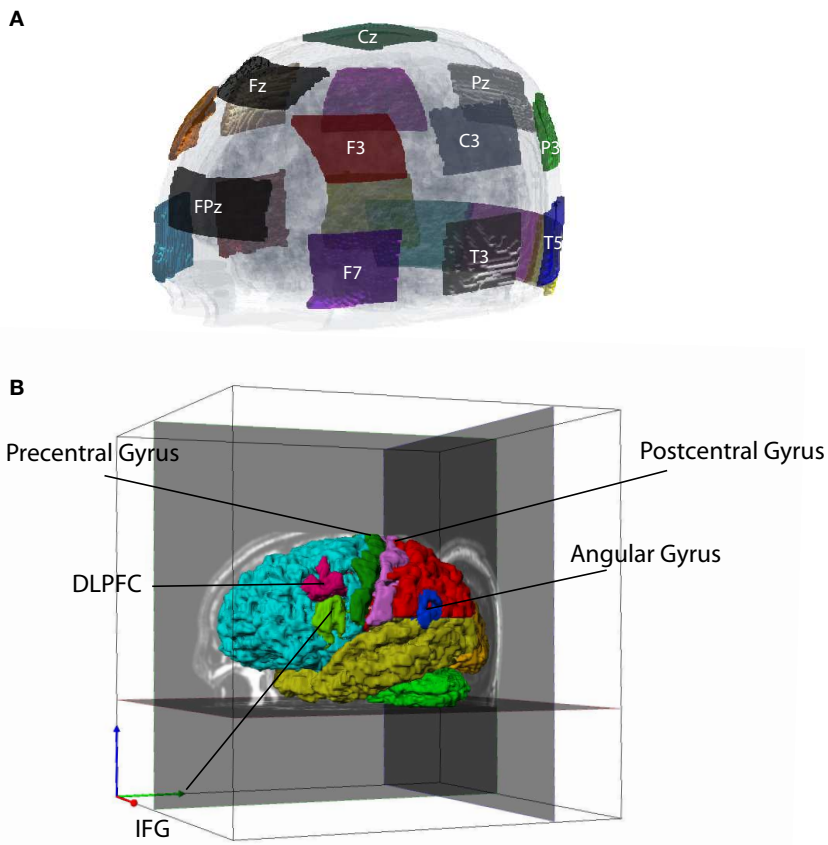


FIGURE 1 | Electrode montage and tissue segmentation. (A) Left frontal view of electrode montage shown on a transparent head model. There were 19 electrodes in total, not all of which are shown. **(B)** Segmented cortical structures, showing frontal (aqua), parietal (red), temporal (yellow), occipital (orange) lobes, cereballar gray matter (green), angular gyrus (AG, blue), dorsolateral prefrontal cortex (DLPFC, cyan), inferior frontal gyrus (IFG, light green), precentral cortex (dark green), and postcentral cortex (pink).

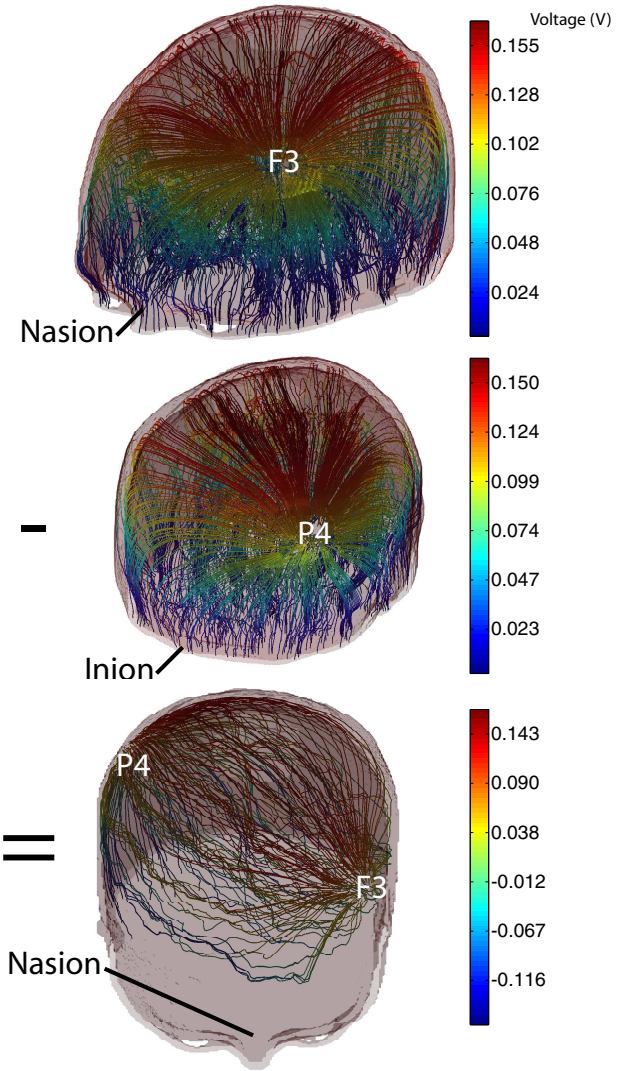


FIGURE 2 | Illustration of addition of 2 base voltage distributions with opposite weights to form a generic 2-electrode tDCS pattern. (Top) Current streamlines formed between the electrode at F3 and model base; (center) current streamlines formed between P4 and model base; (bottom) current streamlines resulting from subtraction of P4 data from F3 data. Streamline colors are indexed to voltage values.

DATA COMPUTATION

Voltage distributions for a particular electrode combination were computed using the principle of superposition by summing the weighted basis data set as

$$V_X = X_1 V_1 + X_2 V_2 + \cdots + X_{NE} V_{NE} \tag{3}$$

where $\boldsymbol{X} = [X_1 X_2 \ldots X_{NE}]$ was a vector of weighting factors for each voltage data set, $V_{1\ldots NE}$ were the basis data sets, and V_X was the resulting voltage. **Figure 2** shows the result of weighted summation of voltage basis data using electrodes F3 and P4. The top and center panels of **Figure 2** show individual voltage basis data for electrodes F3 and P4, and the lower panel shows the result of adding data for electrode F3 (weight 1 mA) to data for P3 (weight −1 mA). The total current magnitude injected into the head was computed as

$$C_{\text{total}} = \frac{1}{2}\sum_{i=1}^{NE} |X_i| \tag{4}$$

The current density $\mathbf{J}$ in each voxel k was calculated as

$$J_k = -\boldsymbol{D}_k \nabla\phi \tag{5}$$

where $\nabla\phi$ is the local voltage gradient.

Current density norms J were calculated within each voxel from individual vector components as

$$J = \left(J_x^2 + J_y^2 + J_z^2\right)^{1/2} \tag{6}$$

This distribution was then used to compute mean or median current densities within regions of interest.

OPTIMIZATION PROCEDURE

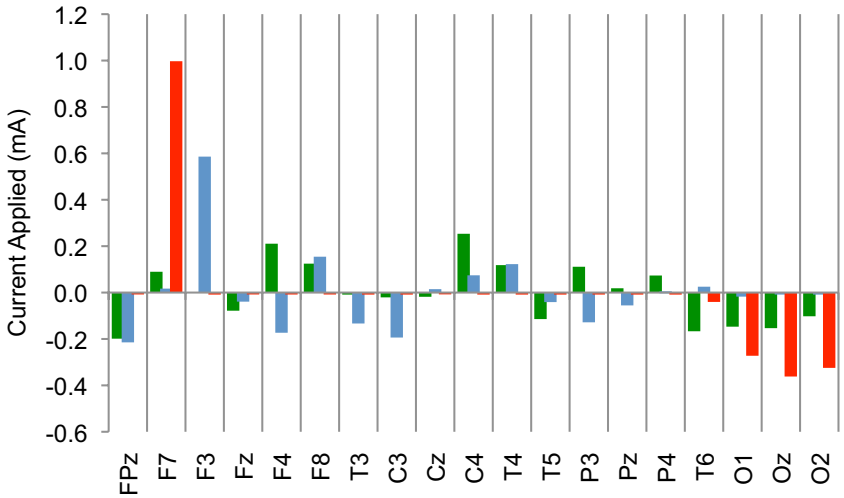
We used the interior point optimization method to calculate the optimal electrode currents. The interior point algorithm (Waltz et al., 2006) solves a general non-linear minimization problem subject to linear and non-linear constraints. Other methods for solving such problems include sequential quadratic programming methods (Bonnans et al., 2006) and simulated annealing (Kirkpatrick et al., 1983).

Our interior point optimization algorithm was implemented in the MATLAB (Natick, MA, USA) function `fmincon` to solve.

$$\max_X \left[\text{mean}\left(J_{\text{target}}(\boldsymbol{X})\right)\right],$$

$$\text{such that} \begin{cases} \sum_{i=1}^{NE} X_i = 0 & (1) \\ \text{mean}\left(J_{\text{avoid}}(\boldsymbol{X})\right) < J_{\max} & (2) \\ \sum_{i=1}^{NE} |X_i| > C_{\min} & (3) \\ \sum_{i=1}^{NE} |X_i| < C_{\max} & (4) \\ \text{mean}\left(J_{\text{target}}(\boldsymbol{X})\right) \geq r\ \text{mean}\left(J_{\text{avoid}}(\boldsymbol{X})\right) & (5) \end{cases} \tag{7}$$

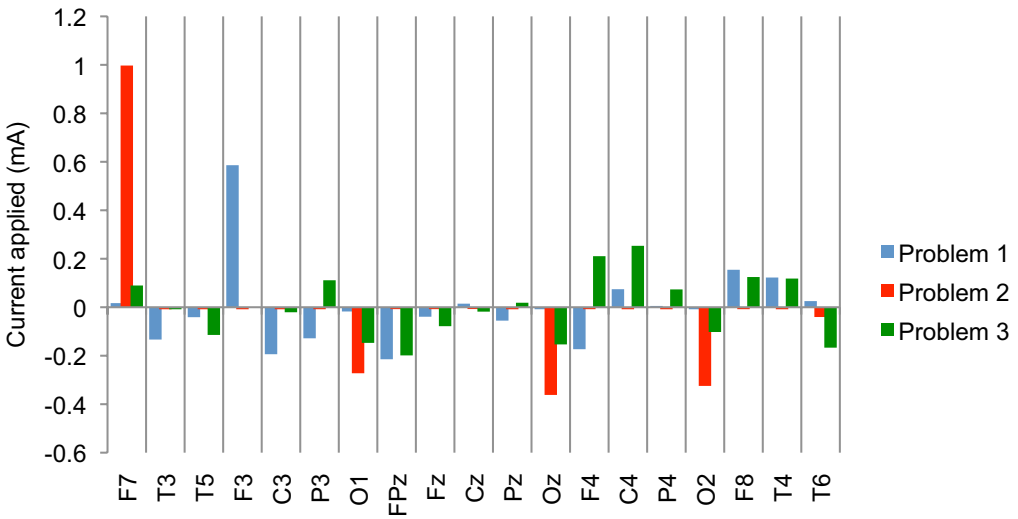
Here, $\boldsymbol{X}$ is the vector consisting of coefficients denoting the stimulus intensity to be delivered to each electrode, and J refers to the current density norm within a brain structure (a *target* region or a region to *avoid*). The quantity $\max_X \left[\text{mean}(J_{\text{target}}(\boldsymbol{X}))\right]$ is the objective function. The optimization is subject to the constraints that the total current injected into the brain is zero (constraint 1), the mean J delivered to the "avoid" region is less than a prescribed maximum value ($J_{\max}$, constraint 2), the total absolute delivered current is above a set threshold ($C_{\min}$, constraint 3) and below another threshold ($C_{\max}$, constraint 4), and the mean J in the target region is at least r times the mean current density in the avoid region, where r is a dimensionless constant (constraint 5). Only constraint 4 is essential. For example, if constraint 1 is not



Electrode (A-P)

Problem \ Electrode	FPz	F7	F3	Fz	F4	F8	T3	C3	Cz	C4
1	-0.215	0.017	0.586	-0.039	-0.173	0.155	-0.133	-0.194	0.015	0.074
2	0.001	0.997	0.000	0.001	0.000	0.000	0.000	0.000	0.001	0.000
3	-0.199	0.090	0.000	-0.078	0.211	0.125	-0.001	-0.021	-0.018	0.253

Problem \ Electrode	T4	T5	P3	Pz	P4	T6	O1	Oz	O2
1	0.123	-0.041	-0.128	-0.055	0.005	0.025	-0.017	0.000	-0.004
2	0.000	0.000	0.000	0.000	0.000	-0.040	-0.272	-0.362	-0.325
3	0.118	-0.114	0.111	0.019	0.074	-0.167	-0.147	-0.153	-0.102



Electrode (L-R)

Problem \ Electrode	F7	T3	T5	F3	C3	P3	O1	FPz	Fz	Cz
1	0.017	-0.133	-0.041	0.586	-0.194	-0.128	-0.017	-0.215	-0.039	0.015
2	0.997	0.000	0.000	0.000	0.000	0.000	-0.272	0.001	0.001	0.001
3	0.090	-0.001	-0.114	0.000	-0.021	0.111	-0.147	-0.199	-0.078	-0.018

Problem \ Electrode	Pz	Oz	F4	C4	P4	O2	F8	T4	T6
1	-0.055	0.000	-0.173	0.074	0.005	-0.004	0.155	0.123	0.025
2	0.000	-0.362	0.000	0.000	0.000	-0.325	0.000	0.000	-0.040
3	0.019	-0.153	0.211	0.253	0.074	-0.102	0.125	0.118	-0.167

FIGURE 3 | Optimized current weights (in mA) found in the three problems, shown in graphical and tabular format. Weights are displayed in (top) Anterior-Posterior and (bottom) Left-Right arrangements.

applied, any unbalanced flow of current through the ground plane may be considered as flow to or from an extracranial electrode, such as those used in several previous studies (Cogiamanian et al., 2007; Monti et al., 2008; Priori et al., 2008). We may consider other constraints, such as a limit on the maximum skin J.

Termination criteria

The optimization procedure was terminated if more than 100 iterations were required, if the relative step size of any iteration was below 1 part in 10^{10} or if the gradient estimate was below 1 part in 10^3. A feasible solution was considered achieved if the maximum constraint violation was smaller than 1 part in 10^{10}.

Mean and median current density values

Although we have previously (Sadleir et al., 2010) quoted median current densities as best representative of distributions, and have observed that the current density distributions are approximately log-normal, there is no analytical method to associate the median of sums and the sum of medians for log-normal distributions (Limpert et al., 2001). This limitation prevents us from associating median current densities in individual base current distributions with the median of their sum. Consequently, the gradient of the objective function cannot be computed, except numerically. Numerical gradient estimation requires many extra function estimations and greatly slows the optimization algorithm. We therefore estimated the gradient of the objective function by computing the mean J created in the target region for each of the 19 candidate patterns. This approach does not produce an exact gradient, but the sum of weighted mean current densities is greater than or equal to actual mean J values, that is

$$
\begin{aligned}
&J = |\boldsymbol{J}| \le X_1 |\boldsymbol{J_1}| + X_2 |\boldsymbol{J}_2| + \cdots + X_{NE} |\boldsymbol{J}_{NE}|\,,\\
&J_{\text{target,avoid}} = \left|\boldsymbol{J}_{\text{target,avoid}}\right| \le X_1 \left|\boldsymbol{J}_1^{\text{target,avoid}}\right| + X_2 \left|\boldsymbol{J}_2^{\text{target,avoid}}\right|\\
&+ \cdots + X_{NE} \left|\boldsymbol{J}_{NE}^{\text{target,avoid}}\right| \text{ and}\\
&\text{mean}(J) \le \text{mean}\,(X_1 |\boldsymbol{J_1}|) + \text{mean}\,(X_2 |\boldsymbol{J}_2|) + \cdots\\
&+ \text{mean}\,(X_{NE} |\boldsymbol{J}_{NE}|) \text{ or}\\
&\text{mean}\left(J_{\text{target,avoid}}\right) \le \text{mean}\left(X_1 \left|\boldsymbol{J}_1^{\text{target,avoid}}\right|\right) + \text{mean}\\
&\left(X_2 \left|\boldsymbol{J}_2^{\text{target,avoid}}\right|\right) + \cdots + \text{mean}\left(X_{NE} \left|\boldsymbol{J}_{NE}^{\text{target,avoid}}\right|\right). \qquad (8)
\end{aligned}
$$

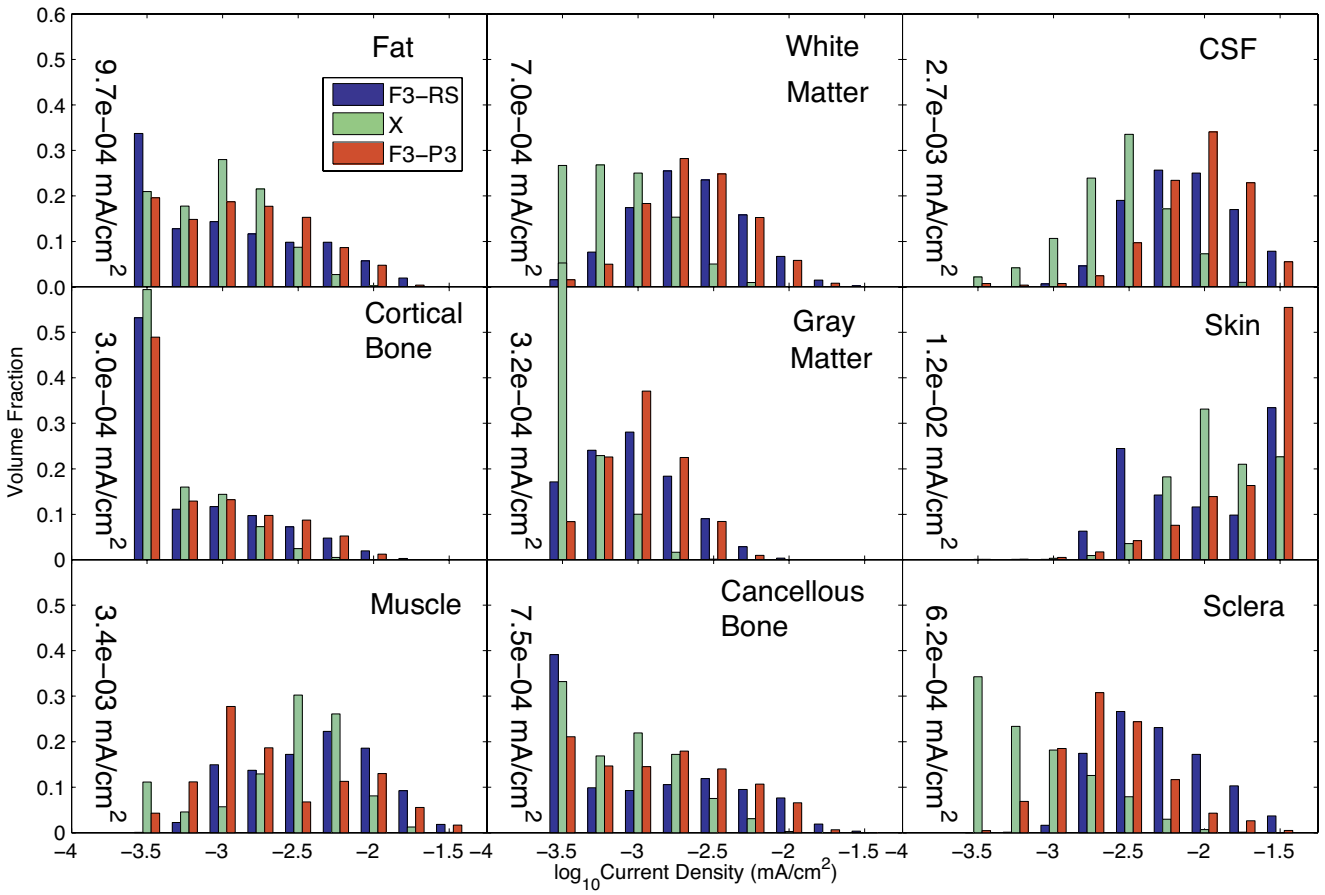


FIGURE 4 | Comparison of current density distributions formed by three candidate current patterns (the optimal solution to Problem 1, X; a configuration previously used in the literature (F3-RS); and a configuration formed using the two electrodes with the largest weights of X. Median values found in each tissue for the optimal solution **(X)** are shown within each graph of the figure.

In the first step of the optimization algorithm, our precomputed gradient was compared with internal estimations of gradient and found to agree within a relative tolerance of 1×10^{-6}. Thus, we believe that the precomputed gradient provided a satisfactory estimate to guide optimization. In the results that follow, we continue to present our findings in terms of median values.

PROBLEMS CONSIDERED

We tested the optimization procedure in the context of three different problems. First, we sought to deliver current preferentially to the left IFG, while avoiding delivery to the accumbens (Problem 1). In this problem we required that the J_{max} experienced by left and right accumbens was less than 0.5 μA/cm^2, while we chose C_{min} and C_{max} to be 0.5 and 2 mA, respectively. We also required that the mean J in the left IFG was at least twice the mean J in the accumbens ($r = 2$).

In Problem 2, we wished to deliver maximal J to the accumbens. No "avoid" region was nominated, but we again chose C_{min} and C_{max} to be 0.5 and 2 mA, respectively.

In Problem 3, we again nominated the accumbens as the target, but specified that the left IFG be avoided. We set the mean J ratio, r, to be 1. Again, C_{min} and C_{max} were 0.5 and 2 mA, respectively.

RESULTS

PROBLEM 1

We executed Problem 1 using the procedures outlined above and obtained a result **X** that satisfied all constraints. The optimization algorithm was terminated because the step size was smaller than the threshold value of 10^{-10}. First-order optimality was found to be around 10^{-3}. The values of individual coefficients are plotted in **Figure 3**. Note that the positive weights of each electrode were biased toward those near the left IFG, such as F3.

We compared the results of Problem 1 optimization with those achieved for an earlier simulation in which only two electrodes were used [F3 and a right supraorbital (RS) electrode]. We also computed the current densities resulting from an F3-P3 pattern, given that the estimated **X** value contained large coefficients for each of these electrodes. The results for these three configurations are compared in **Figure 4**, showing the current distributions in different tissues. The 1-norm of the total current found for our "optimized" problem, $C = 1.15$ mA, was scaled so that the total injected current had the same value of 1 mA in all three configurations.

The median current density in different tissues found in each of these three configurations is shown in **Table 2**. The current densities in the target and avoided regions are highlighted in green and red respectively.

The current distributions in peripheral cortical tissues are summarized in **Figure 5**. The distributions in the IFG, DLPFC, and angular gyrus are shown bilaterally. The median current densities in the left IFG were approximately four times those in the right IFG.

PROBLEM 2

Solution of Problem 2, which sought to maximize mean current densities in the accumbens with no "avoid" region specified, was terminated because the maximum number of iterations was exceeded. However, substantial progress toward a solution was made. We found that the optimization procedure produced a clear bias toward anterior and posterior electrodes. Also, there were only four electrodes with an absolute normalized weight greater than 1 μA – electrodes F7, O1, O2, Oz, and T6. The electrode with the largest weight, F7, was not centrally located, being on the lower left head, and all other electrodes had negative weights. We believe that this unexpected bias may have resulted from inhomogeneity in the conductivity distribution or white matter directions. The problem resulted in a first-order optimization value of about 2×10^{-3}, larger than the value found in solving Problem 1.

Distribution estimations within basal ganglia and peripheral cortical structures for Problem 2 are plotted in **Figure 6** for the normalized optimized pattern. A comparison with a 2-electrode pattern chosen by using only the electrodes with the two largest

Table 2 | Median current density values found in different tissues and structures for Problem 1.

	X mA/cm^2	F3-RS mA/cm^2	F3-P3 mA/cm^2
TISSUE			
Blood	1.04×10^{-4}	4.45×10^{-3}	4.85×10^{-4}
Cancelous bone	7.49×10^{-5}	8.04×10^{-4}	1.32×10^{-4}
Cortical bone	2.97×10^{-5}	3.66×10^{-4}	4.41×10^{-5}
CSF	2.75×10^{-4}	7.49×10^{-3}	9.36×10^{-4}
Fat	9.67×10^{-4}	8.54×10^{-4}	1.22×10^{-4}
Gray matter	3.21×10^{-4}	9.06×10^{-4}	1.01×10^{-4}
Muscle	3.36×10^{-3}	4.52×10^{-3}	1.53×10^{-4}
Sclera	6.22×10^{-4}	4.65×10^{-3}	2.12×10^{-4}
Skin	1.18×10^{-2}	9.42×10^{-3}	2.80×10^{-3}
White matter	6.98×10^{-4}	2.26×10^{-3}	2.22×10^{-4}
CORTICAL STRUCTURE			
AG (L)	7.20×10^{-4}	9.31×10^{-4}	2.22×10^{-3}
AG (R)	3.10×10^{-4}	5.96×10^{-4}	7.00×10^{-4}
Cingulate	2.88×10^{-4}	9.09×10^{-4}	1.18×10^{-3}
DLPFC (L)	1.13×10^{-3}	1.52×10^{-3}	2.82×10^{-3}
DLPFC (R)	3.26×10^{-4}	1.68×10^{-3}	9.78×10^{-4}
Frontal lobe	4.39×10^{-4}	2.07×10^{-3}	1.31×10^{-3}
IFG (L)	8.26×10^{-4}	1.87×10^{-3}	2.14×10^{-3}
IFG (R)	2.63×10^{-4}	1.49×10^{-3}	7.73×10^{-4}
Occipital lobe	3.14×10^{-4}	3.84×10^{-4}	8.89×10^{-4}
Parietal lobe	3.92×10^{-4}	6.45×10^{-4}	1.20×10^{-3}
Temporal lobe	3.49×10^{-4}	8.72×10^{-4}	8.93×10^{-4}
DEEP STRUCTURE			
Accumbens	9.74×10^{-5}	1.38×10^{-3}	9.08×10^{-4}
Amygdala	2.19×10^{-4}	1.37×10^{-3}	1.18×10^{-3}
Caudate nucleus	1.66×10^{-4}	1.70×10^{-3}	9.13×10^{-4}
Cerebellar GM	2.03×10^{-4}	4.06×10^{-4}	4.92×10^{-4}
Hippocampus	2.46×10^{-4}	1.15×10^{-3}	8.91×10^{-4}
Globus pallidus	1.65×10^{-4}	1.20×10^{-3}	9.26×10^{-4}
Putamen	2.06×10^{-4}	1.37×10^{-3}	8.70×10^{-4}
Thalamus	2.01×10^{-4}	1.03×10^{-3}	1.02×10^{-3}

*The optimal weighting **X** was compared with another candidate pattern (F3-RS) and a pattern found using the 2 greatest weights in **X**. Median values in targeted and avoided regions are highlighted in green and red shading, respectively.*

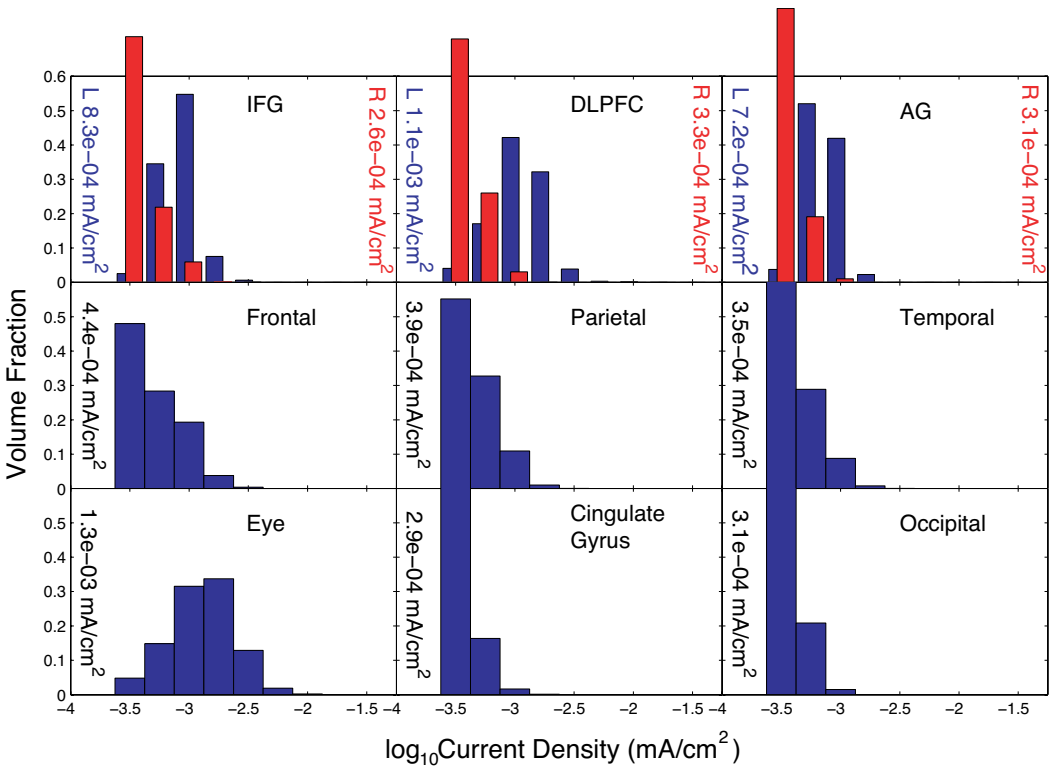


FIGURE 5 | Distribution of current densities in peripheral cortical structures in Problem 1 found using the optimal solution, X. Median values in each structure obtained using the optimal solution are shown within each graph of the figure. IFG, DLPFC, and AG refer to the inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), and angular gyrus (AG), respectively. For the IFG, DLPFC, and AG, current density distributions are shown separately for left (blue) and right (red) structures, with median values shown on either side of each plot.

magnitude weights found by the optimization procedure, F7 and Oz, is shown in **Table 3**. The current densities found in target structures by the optimization procedure (using five electrodes) were very similar to this 2-electrode pattern. Median eye current densities found for both the F7-Oz pattern and the optimal solution were around 10 $\mu A/cm^2$. The threshold for phosphene generation cited in the literature (8 mA/m^2 or 0.8 $\mu A/cm^2$; Reilly, 1998) was based on stimulation at 20 Hz. Therefore, even though the threshold for DC stimulation might in fact be at least a factor of 10 higher (Adrian, 1977), we would expect this current pattern to produce phosphenes.

A test performed using the F7-Oz pattern as an initial point for the procedure resulted in no progress toward the final solution. Interestingly, the first-order optimality measure found using F7-Oz was 3.5×10^{-3}, larger than that found for the final value of **X** for Problem 2, which was around 2×10^{-3}.

PROBLEM 3

The pattern found when the IFG was specified as the "avoid" region was biased toward electrodes on the right side of the head, as expected. Execution of Problem 3 was terminated because the step size decreased below threshold. Results for the normalized optimized pattern are shown in **Figure 7** for peripheral and deep structures. **Table 4** shows median values in different structures for this pattern and for a 2-electrode pattern found by combining the electrodes that had the two largest magnitude weights in **X**–C4 and FPz. Current densities found in the right cortex were generally larger than those in the left cortex or deep brain structures. Median current densities in the eye for this case were larger than in Problem 2 (around 7×10^{-2} mA/cm^2), and therefore phosphene generation would be highly likely with this configuration.

USE OF FEWER THAN 19 ELECTRODES

Results obtained by the optimization, with approximate normalized "optimal" patterns created using the 2-, 4-, and 6-highest magnitude current electrodes are shown in **Table 5**, now comparing target and avoid regions for each pattern. In this test, if the sum of currents from the set of electrodes was found to be non-zero (contrary to constraint 1), we assumed that remaining current flowed to an extracranial electrode. These electrode patterns resulted in distributions in the target or avoid structures being of the same magnitude as those found using the full 19-electrode montage.

DISCUSSION

The solution of problem 1 demonstrates how an optimization approach might be used to allow more efficient and precise targeting of tDCS currents to nominated brain regions and enable steering of current away from other specified areas in individual subjects. The solution we found for this problem successfully

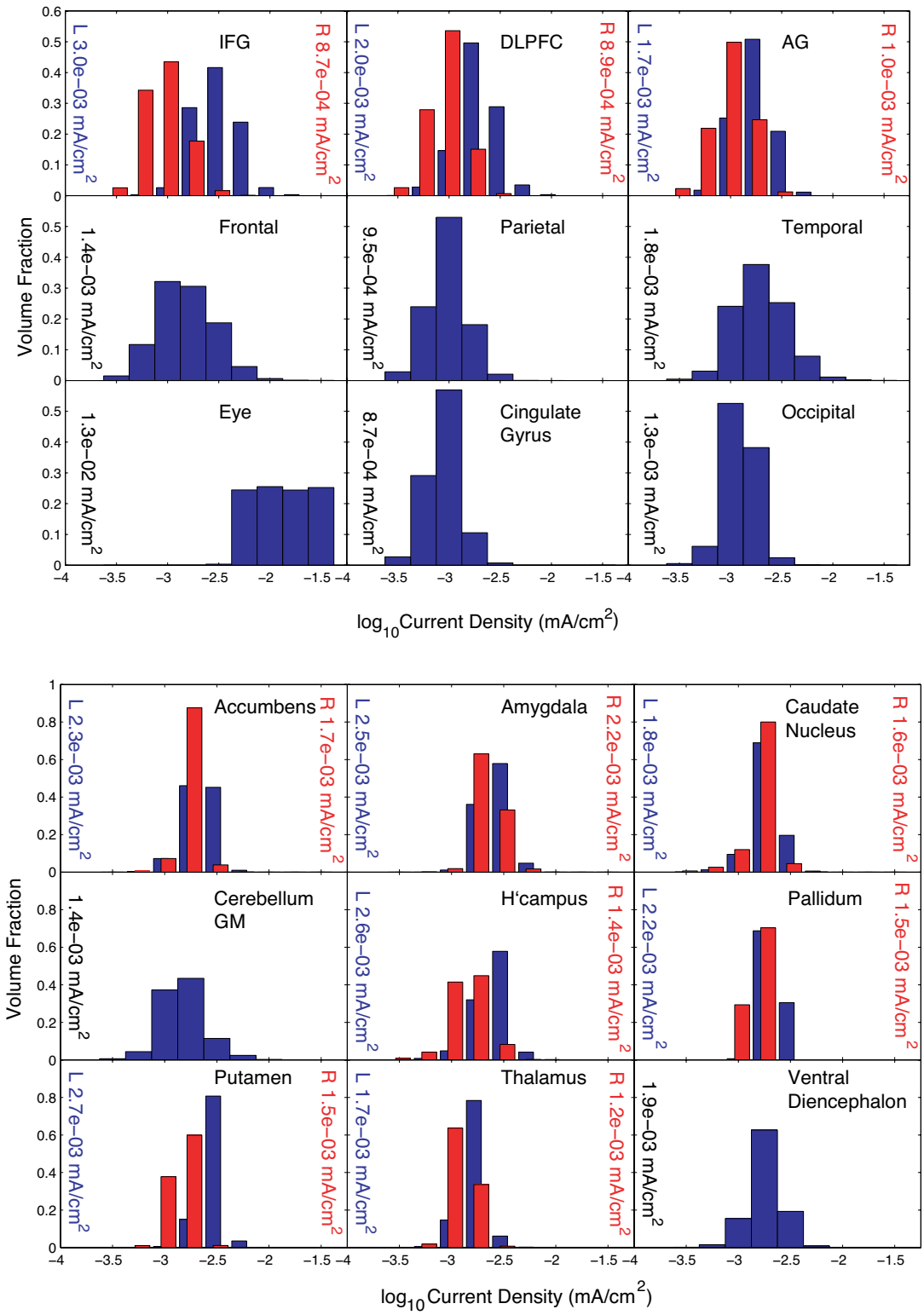


FIGURE 6 | Distribution of current densities in (top) peripheral cortical structures and (bottom) deep brain structures for Problem 2. Median values in each structure obtained using the optimal solution **X** are shown within each graph of the figure. IFG, DLPFC, and AG refer to the inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), and angular gyrus (AG), respectively. For the IFG, DLPFC, and AG, current density distributions are shown separately for left (blue) and right (red) structures, with median values shown on either side of each plot.

directed current away from the accumbens (producing a bilateral median current density of 9.74×10^{-5} mA/cm^2) and producing a median current density in the IFG of 8.26×10^{-4} mA/cm^2 in the IFG target. By comparison, the two alternative current patterns, F3-RS and F3-P3, although producing larger current densities in the IFG, both produced median current densities in the accumbens that were at least a factor of 10 larger. The ability to selectively deliver current to different structures may therefore facilitate experiments relating to the structures and mechanisms involved in tDCS effects, particularly when implemented using subject-specific models. Further, use of distributed (i.e., more than two electrodes) current patterns may reduce skin currents and the likelihood of peripheral nerve stimulation and therefore provide a safety benefit over other patterns.

USE OF FEWER ELECTRODES

It may also be that patterns using fewer electrodes, based on these "optimal" designs, can be achieved, as demonstrated in Section "Use of Fewer Than 19 Electrodes." These patterns could be implemented by coupling several current generators together. Use of a selection of higher weighted electrodes in combination with a single extracranial electrode might provide a practical method of implementing computed patterns.

SAFETY CONSIDERATIONS

The maximal skin currents shown in **Table 5** were reduced as more electrodes were incorporated. Therefore, use of more electrodes may make it possible to apply a larger total current and achieve some current steering without causing peripheral nerve stimulation. The nominal current density value thought to produce peripheral nerve stimulation is about 0.1 mA/cm^2 (Reilly, 1998). Note that in all but one case shown in **Table 5**, the predicted maximum skin current densities were above this limit. However, these current densities were observed in very small volumes near electrodes, and it is unclear whether these patterns would actually result in a subject's perception of the current. In the two problems targeting deep structures, we observed median eye currents of the order of 0.1 mA/cm^2. This prediction implies that phosphene generation is likely using these patterns. Use of the eye as an "avoid" region might produce more acceptable patterns.

USE OF MORE CONSTRAINTS

The problems we have considered here involve a fixed amount of current applied to the head. This current must flow somewhere. Use of "avoid" constraints may result in large currents being observed in areas that are neither avoided nor target regions, such as those found in right peripheral cortical regions in Problem 3. This issue will obviously be more prevalent as more avoided regions are chosen and will depend on the relative geometry of electrodes, avoided regions, and target regions. We expect that it may not be possible to solve some over constrained optimization tasks, or to find a feasible starting point.

A corollary finding is that these observations may be beneficial and provide alternatives to previous stimulation protocols. For example, the median J found in the left IFG by Problem 2 was larger than that found using the F3-RS current pattern, which has been presumed appropriate for stimulating this area. If applying a large current to the left IFG is the only requirement, then a pattern similar to that found in Problem 2 might also be considered to stimulate the IFG of a similar subject.

Table 3 | Median current density values found in different tissues and structures for Problem 2.

	X mA/cm^2	**FPz-Oz** mA/cm^2	**F7-Oz** mA/cm^2
TISSUE			
Blood	6.00×10^{-3}	5.94×10^{-3}	6.07×10^{-3}
Cancelous bone	6.89×10^{-4}	6.69×10^{-4}	6.81×10^{-4}
Cortical bone	6.09×10^{-4}	3.42×10^{-4}	5.76×10^{-4}
CSF	1.00×10^{-2}	1.21×10^{-2}	1.02×10^{-2}
Fat	1.09×10^{-3}	8.46×10^{-4}	9.90×10^{-4}
Gray matter	1.38×10^{-3}	1.36×10^{-3}	1.40×10^{-3}
Muscle	6.84×10^{-3}	3.56×10^{-3}	6.78×10^{-3}
Sclera	7.47×10^{-3}	6.58×10^{-3}	7.53×10^{-3}
Skin	1.14×10^{-2}	8.38×10^{-3}	1.11×10^{-2}
White matter	6.92×10^{-3}	2.81×10^{-3}	6.96×10^{-3}
CORTICAL STRUCTURE			
AG (L)	1.69×10^{-3}	1.27×10^{-3}	1.70×10^{-3}
AG (R)	1.00×10^{-3}	1.27×10^{-3}	9.80×10^{-4}
Cingulate	8.70×10^{-4}	1.07×10^{-3}	8.86×10^{-4}
DLPFC (L)	1.99×10^{-3}	1.86×10^{-3}	2.00×10^{-3}
DLPFC (R)	8.92×10^{-4}	1.71×10^{-3}	8.92×10^{-4}
Frontal lobe	1.44×10^{-3}	1.82×10^{-3}	1.45×10^{-3}
IFG (L)	3.03×10^{-3}	1.83×10^{-3}	3.05×10^{-3}
IFG (R)	8.73×10^{-4}	1.62×10^{-3}	8.75×10^{-4}
Occipital lobe	1.26×10^{-3}	1.12×10^{-3}	1.32×10^{-3}
Parietal lobe	9.47×10^{-4}	9.72×10^{-4}	9.50×10^{-4}
Temporal lobe	1.85×10^{-3}	1.44×10^{-3}	1.87×10^{-3}
DEEP STRUCTURE			
Accumbens (L)	2.33×10^{-3}	1.46×10^{-3}	2.34×10^{-3}
Accumbens (R)	1.74×10^{-3}	1.42×10^{-3}	1.75×10^{-3}
Amygdala	2.37×10^{-3}	1.95×10^{-3}	2.39×10^{-3}
Caudate nucleus	1.70×10^{-3}	1.26×10^{-3}	1.71×10^{-3}
Cerebellar GM	1.43×10^{-3}	1.40×10^{-3}	1.46×10^{-3}
Hippocampus	2.01×10^{-3}	1.52×10^{-3}	2.03×10^{-3}
Globus pallidus	1.80×10^{-3}	1.32×10^{-3}	1.82×10^{-3}
Putamen	2.06×10^{-3}	1.23×10^{-3}	2.07×10^{-3}
Thalamus	1.42×10^{-3}	1.48×10^{-3}	1.43×10^{-3}

*The optimal weighting **X** is compared with a symmetric pattern (FPz-Oz) and a pattern found using the 2 greatest weights in **X** (F7-Oz). Median values in the targeted region are highlighted in green shading.*

OPTIMALITY

The results we have found have satisfied the requirements specified to the optimization algorithm, with some exceptions. However, there is no guarantee that the solution is a global optimum or even unique. A trivial demonstration of the non-uniqueness of solutions is that exactly the same current densities as any candidate weighting, $\mathbf{X}$, will be produced by $-\mathbf{X}$, since most constraints and objective function are based solely on current density magnitude. This lack of uniqueness could be resolved by introducing a

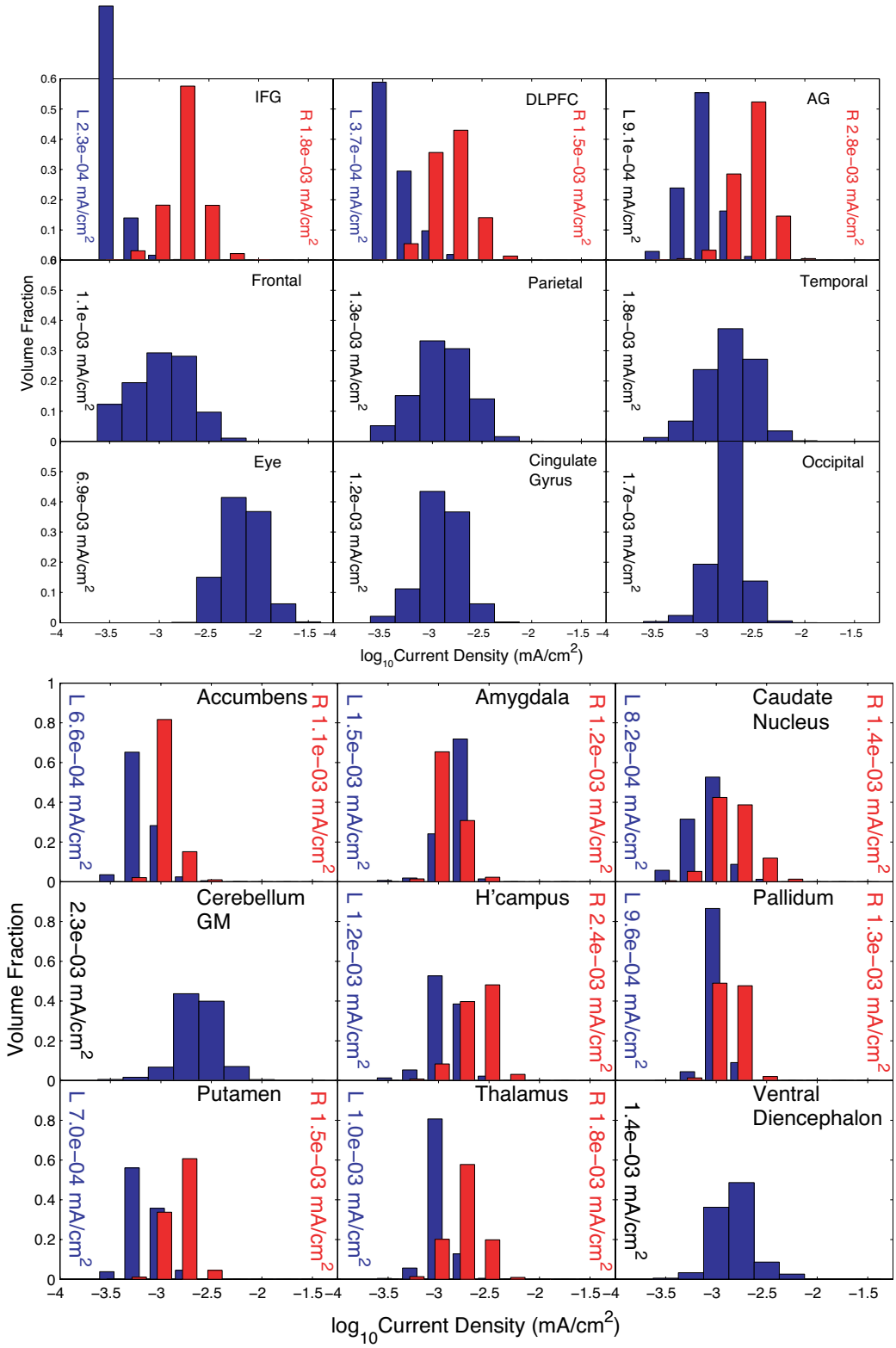


FIGURE 7 | Distribution of current densities in (top) peripheral cortical structures and (bottom) deep brain structures for Problem 3. Median values in each structure obtained using the optimal solution **X** are shown within each graph of the figure. IFG, DLPFC, and AG refer to the inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), and angular gyrus (AG), respectively. For the IFG, DLPFC, and AG, current density distributions are shown separately for left (blue) and right (red) structures, with median values shown on either side of each plot.

Table 4 | Median current density values found in different tissues and structures for Problem 3.

	X mA/cm^2	C4-FPz mA/cm^2
TISSUE		
Blood	5.31×10^{-4}	4.67×10^{-3}
Cancelous bone	1.66×10^{-3}	1.31×10^{-3}
Cortical bone	7.18×10^{-4}	3.42×10^{-4}
CSF	1.00×10^{-2}	9.91×10^{-3}
Fat	2.41×10^{-3}	1.25×10^{-3}
Gray matter	1.48×10^{-3}	1.09×10^{-3}
Muscle	7.79×10^{-3}	3.01×10^{-3}
Sclera	2.90×10^{-3}	4.93×10^{-3}
Skin	2.46×10^{-2}	1.58×10^{-2}
White matter	3.09×10^{-3}	2.75×10^{-3}
CORTICAL STRUCTURE		
AG (L)	9.10×10^{-4}	5.48×10^{-4}
AG (R)	2.85×10^{-3}	2.55×10^{-3}
Cingulate	1.24×10^{-3}	1.36×10^{-3}
DLPFC (L)	3.67×10^{-4}	1.67×10^{-3}
DLPFC (R)	1.46×10^{-3}	2.82×10^{-3}
Frontal lobe	6.89×10^{-3}	1.94×10^{-3}
IFG (L)	2.28×10^{-4}	1.43×10^{-3}
IFG (R)	1.76×10^{-3}	2.11×10^{-3}
Occipital lobe	1.69×10^{-3}	6.92×10^{-4}
Parietal lobe	1.26×10^{-3}	1.03×10^{-3}
Temporal lobe	1.79×10^{-3}	7.06×10^{-4}
DEEP STRUCTURE		
Accumbens (L)	6.56×10^{-4}	1.00×10^{-3}
Accumbens (R)	1.11×10^{-3}	1.36×10^{-4}
Amygdala	1.37×10^{-3}	1.19×10^{-3}
Caudate nucleus	1.04×10^{-3}	1.12×10^{-3}
Cerebellum GM	2.31×10^{-3}	7.04×10^{-4}
Hippocampus	1.57×10^{-3}	7.85×10^{-4}
Globus pallidus	1.16×10^{-3}	8.97×10^{-4}
Putamen	1.12×10^{-3}	9.93×10^{-4}
Thalamus	1.27×10^{-3}	9.91×10^{-4}

*The optimal weighting **X** is compared with a pattern found using the 2 greatest weights in X (C4-Pz). Median values in targeted and avoided regions are highlighted in green and red shading, respectively.*

Table 5 | Comparison of effects of using 2-, 4- and 6-electrode patterns based on optimal current patterns.

	X2 mA/cm^2	X4 mA/cm^2	X6 mA/cm^2	X19 mA/cm^2
PROBLEM 1				
IFG (L)	2.19×10^{-3}	1.77×10^{-3}	1.46×10^{-3}	8.26×10^{-4}
IFG (R)	1.25×10^{-3}	1.33×10^{-3}	1.24×10^{-3}	2.63×10^{-4}
Accumbens (L)	1.55×10^{-3}	1.41×10^{-3}	1.22×10^{-3}	9.74×10^{-5}
Accumbens (R)	1.41×10^{-3}	1.31×10^{-3}	1.13×10^{-3}	2.19×10^{-4}
Skin maximum	3.17×10^{-1}	2.24×10^{-1}	1.80×10^{-1}	2.41×10^{-1}
PROBLEM 2				
IFG (L)	3.02×10^{-3}	3.05×10^{-3}	–	3.03×10^{-3}
IFG (R)	9.06×10^{-4}	8.75×10^{-4}	–	8.73×10^{-4}
Accumbens (L)	2.35×10^{-3}	2.34×10^{-3}	–	2.33×10^{-3}
Accumbens (R)	1.77×10^{-3}	1.75×10^{-3}	–	1.74×10^{-3}
Skin maximum	4.26×10^{-1}	4.24×10^{-1}	–	4.18×10^{-1}
PROBLEM 3				
IFG (L)	8.25×10^{-4}	9.50×10^{-4}	6.97×10^{-4}	2.28×10^{-4}
IFG (R)	1.91×10^{-3}	1.38×10^{-3}	1.03×10^{-3}	1.76×10^{-3}
Accumbens (L)	1.15×10^{-3}	9.96×10^{-4}	7.59×10^{-4}	6.56×10^{-4}
Accumbens (R)	1.23×10^{-3}	9.90×10^{-4}	7.53×10^{-4}	1.11×10^{-4}
Skin maximum	2.34×10^{-1}	1.32×10^{-1}	9.71×10^{-2}	2.31×10^{-1}

Medians in targeted and avoided regions are highlighted in green and red shading, respectively. Maximum skin current densities are also shown for each pattern.

constraint on a single electrode, *i*, that restricted its coefficient, X_i, to be either less than or greater than zero.

The optimality measure produced by the algorithm, a numerical measure of the gradient of the objective function at each iteration, was found to be less than 10^{-3} for solution of Problem 1. We know that our gradient estimation is not exact, but this value should provide some indication of the landscape of the objective function. Even if gradient estimation is exact, finding an optimality measure that suggests the objective function is at or near an extreme value does not guarantee that the solution attained is a global minimum.

Solutions in Problems 2 and 3 produced optimality measures of around 2 and 3×10^{-3}, respectively. Solutions in these two problems took many more iterations to produce than in Problem 1, and solution of Problem 2 was terminated because the algorithm required more than 100 iterations. Very similar results to the optimal solution (**X**) to Problem 2 were found using its two principal electrodes, and, in fact, *J* values in the target structure were slightly larger when the two principal electrodes were used. It is possible that the F7-Oz solution is very close to the optimum solution for this Problem, and with this subject model. This finding may also suggest that solutions targeting of deep structures may not be unique, and that there are other possible configurations that satisfy the problem specification.

CONCLUSION

We demonstrated that use of a finite element model of the head, in conjunction with a non-linear optimization procedure, could result in current steering both away from and toward different structures. We found that it was possible to direct current to the left IFG while avoiding the accumbens region; to target current on the basal ganglia exclusively; and to avoid the left IFG while targeting basal ganglia. When deep structures were targeted, it was not possible to avoid delivering current to peripheral cortical regions. Further, use of this methodology revealed asymmetry in structures that may not have easily been found using other strategies. We believe that this or a similar method of optimization may prove useful in further studies of tDCS.

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Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models

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Background: Transcranial Direct Current Stimulation (tDCS) is a non-invasive, versatile, and safe neuromodulation technology under investigation for the treatment of neuropsychiatric disorders, adjunct to rehabilitation, and cognitive enhancement in healthy adults. Despite promising results, there is variability in responsiveness. One potential source of variability is the intensity of current delivered to the brain which is a function of both the operator controlled tDCS dose (electrode montage and total applied current) and subject specific anatomy. We are interested in both the scale of this variability across anatomical typical adults and methods to normalize inter-individual variation by customizing tDCS dose. Computational FEM simulations are a standard technique to predict brain current flow during tDCS and can be based on subject specific anatomical MRI. **Objective:** To investigate this variability, we modeled multiple tDCS montages across three adults (ages 34–41, one female). **Results:** Conventional pad stimulation led to diffuse modulation with maximum current flow between the pads across all subjects. There was high current flow directly under the pad for one subject while the location of peak induced cortical current flow was variable. The High-Definition tDCS montage led to current flow restricted to within the ring perimeter across all subjects. The current flow profile across all subjects and montages was influenced by details in cortical gyri/sulci. **Conclusion:** This data suggests that subject specific modeling can facilitate consistent and more efficacious tDCS.

Keywords: tDCS, head model, HD-tDCS, TMS, tACS, transcranial electrical stimulation

INTRODUCTION

Transcranial Direct Current Stimulation (tDCS) has gained widespread popularity for being a non-invasive, cheap, safe therapy investigated for treating a host of neurological disorders, enhancing cognitive abilities, and as an adjuvant rehabilitation treatment (Nitsche and Paulus, 2000; Antal et al., 2004; Fregni et al., 2006; Edwards et al., 2009; Baker et al., 2010; Loo et al., 2012). During tDCS, the current injected through scalp electrodes induces electric fields (EF) in the cortex which is believed in turn to modulate neuronal excitability (Nitsche and Paulus, 2000). This modulation of membrane excitability ultimately determines observed behavioral/clinical outcomes.

Since its introduction in its current form (Nitsche and Paulus, 2000), there is still limited knowledge of how to optimally determine treatment "dose" – where dose is defined by electrode placement/size or stimulus parameters (current intensity, polarity, session duration) controllable by the operator (Bikson et al., 2008; Peterchev et al., 2011). While, these various dose options underlie the inherent flexibility of tDCS, they also make the optimal choice difficult to ascertain (Brunoni et al., 2012). It is reasonable to assume that cortical regions subject to higher current flow intensities are more likely candidates for modulation and plasticity. Importantly, the distribution of current flow in the brain depends not only on the stimulation dose but underlying anatomy/tissue properties. In this way, the same dose applied to two subjects may result in different brain current flow patterns (Chaieb et al., 2008). Furthermore, the same dose across healthy subjects and subjects with compromised anatomy (lesions, skull defects) may lead to varied brain regions activated by current flow and thus inconsistent clinical outcomes.

It is known that there are age-related anatomical differences spanning the pediatric to the elderly population. Even within a particular age group, there is remarkable inter-individual variability in anatomy both at the level of whole tissue volume/thickness and cortical morphology. For example, brain volume across 30 individuals aged (18–35) was found to vary by as much as 40% (Song et al., 2011). Cortical gyri-sulci morphology (contours, folding patterns, functional localization) are complex and are characterized by high inter-individual variability (Mangin et al., 2004; Derrfuss et al., 2009). This is of particular significance since the gyrated structure of the brain has been implicated in the observance of current "hot-spots" in high-resolution modeling (see supplementary figure – Datta et al., 2009). Furthermore, studies have suggested gender-related differences: (1) males have higher CSF and white matter volume while females have higher gray matter volume (Gur et al., 2002) and (2) females might have thicker skulls than men. It remains to be seen whether these aforementioned differences may translate to

a significant difference in tDCS current flow patterns across individuals.

Computational modeling using finite element (FE) methods is an established tool for predicting tDCS current flow and thus should be leveraged to plan dosing strategies. Recent studies have attempted to directly compare modeling predictions to clinical outcomes thereby validating the utility of this approach (Mendonca et al., 2011; Dasilva et al., 2012; Turkeltaub et al., 2012). In addition, we have recently used patient-specific modeling for tDCS responders to: (a) retrospectively analyze the success of a given montage in aphasia stroke (Datta et al., 2011) and (b) compared model predictions to physiological patterns of activation revealed by fMRI in visual stroke (Halko et al., 2011).

Transcranial direct current stimulation studies are usually planned by assuming increased/decreased excitability "under" the anode/cathode electrode respectively or by placing the active electrode "over" the desired region-of-interest with the return electrode placed on a distant location – contralateral hemisphere or at extra cephalic locations. The increased proliferation of studies over the last decade has shown that this heuristic strategy has proven efficacious. But this simple approach is not consistent with imaging/modeling studies which suggest broad neuronal activation with peak brain modulation potentially between electrodes (Lang et al., 2005; Datta et al., 2009; Sadleir et al., 2010; Salvador et al., 2010). One source of observed variability across subjects could therefore be variation in the location of peak brain current flow as well as overall current flow patterns.

As a first step toward considering the impact of anatomical differences in resulting brain current flow across healthy adults, we modeled tDCS induced electrical fields in three adults: two males (M1, M2) and one female (F) via high spatial resolution (1 mm^3) gyri-sulci precise computer modeling. The magnitude and the spatial extent of conventional sponge-pad and High-Definition (HD)-tDCS were compared across subjects (Datta et al., 2009; Borckardt et al., 2012). HD montages allow focal delivery of current to select regions of the cortex. We report that tDCS modulation maps may be fundamentally influenced by the underlying individual head anatomy.

MATERIALS AND METHODS

We obtained T1 and T2 scans at 1 mm^3 resolution from three healthy neurologically normal subjects: Male 1 (M1): 36 years; Male 2 (M2): 41 years and Female (F): 34 years. Automated segmentation was first performed using SPM (Ashburner, 2009) to demarcate the MRI images into six tissue categories: skin, skull, CSF, gray matter, white matter, and air. An in-house MATLAB script (Huang et al., 2012) was used to correct for the automatic segmentation errors. Residual segmentation errors were finally fixed in ScanIP (Simpleware, Ltd., Exeter, UK) using a combination of segmentation tools (point to point line, smoothing filters, and Boolean operations). The stimulation electrodes were created as CAD files and were positioned interactively within the image data (**Figure 1**). Adaptive FE meshes were generated with a minimum quality factor of 0.4 from the segmentation and the CAD masks (Simpleware). The entire workflow preserved the resolution of the anatomical 1 mm resolution data (Bikson and Datta, 2012). The meshes were imported to COMSOL Multiphysics 3.5a (Burlington, MA, USA) for FE computation and comprised >10 million elements with >15 million degrees of freedom. Electrical conductivities (S/m) were assigned the representative average values obtained from literature: Skin (0.465); Skull (0.01); CSF (1.65); Gray matter (0.276); White matter (0.126); air (1e−7); electrode (5.8e7); sponge (1.4); gel (0.3) (Wagner et al., 2007).

The two modeled electrode configurations for each of the three heads were as follows:

(1) Conventional "rectangular-pad"– Two electrode-sponge pads (5 cm × 5 cm) were placed at sites commonly used for the classic motor cortex-contralateral orbital stimulation (**Figure 1**). Typically sponges are soaked in saline for tDCS application – sponges were thus assigned saline's conductivity and the abutting electrode energized.
(2) HD 4 × 1-ring – Four cathode disk electrodes were arranged in a circular fashion around an anode center electrode (Datta et al., 2009; Borckardt et al., 2012). The anode electrode is placed over the motor cortex coinciding with the center of the anode pad used for conventional stimulation (**Figure 1**). All electrodes had a diameter of 12 mm and an electrode-center to electrode-center distance of 6 cm from the central anode electrode was used. Current was conducted into the head via a gel.

The standard Laplace equation was solved using conjugate gradients iterative solver with a tolerance of 1×10^{-6}. 1 mA total current was applied at the anode electrode and ground was applied at the negative electrode(s). The remaining external surfaces were considered as insulated. Cortical EF surface and cross-section magnitude maps were determined (**Figures 2** and **3**). The surface EF magnitude maps were plotted to the respective induced peak on the cortical surface. In addition, directional plots normal to the cortical surface (inward or outward) were plotted (Datta et al., 2008; Turkeltaub et al., 2012).

RESULTS

For the conventional 5 × 5 pad tDCS and the 4 × 1-ring HD-tDCS configurations, we calculated induced cortical EF across all subjects. The surface/cross-section magnitude plots for each combination (montage and subject) allow a direct comparison of the spatial profile and depth focality. In addition, the role of inter-individual differences is further demonstrated by the consideration of current flow direction and zoomed views of a region-of-interest (motor strip). Barring the zoomed views, each of the false-color plots have been plotted to the respective peak EF induced on the cortical surface.

CONVENTIONAL PAD STIMULATION

Conventional pad stimulation resulted in current clustering with diffuse modulation over wide parts of the cortex (**Figures 2A.1, B.1,C.1**). The top view (**Figures 2A.3,B.3,C.3**) together with the right side view (**Figures 2A.4,B.4,C.4**) further highlight the widespread nature of current flow across the entire cortical surface. This is attributable to the large size/separation of the pads and gyrated anatomy. Consistent with previous predictions, the overall current flow was complex, reflecting the convoluted gyri-sulci morphology and individual neuroanatomy (Datta et al., 2009, 2011; Salvador

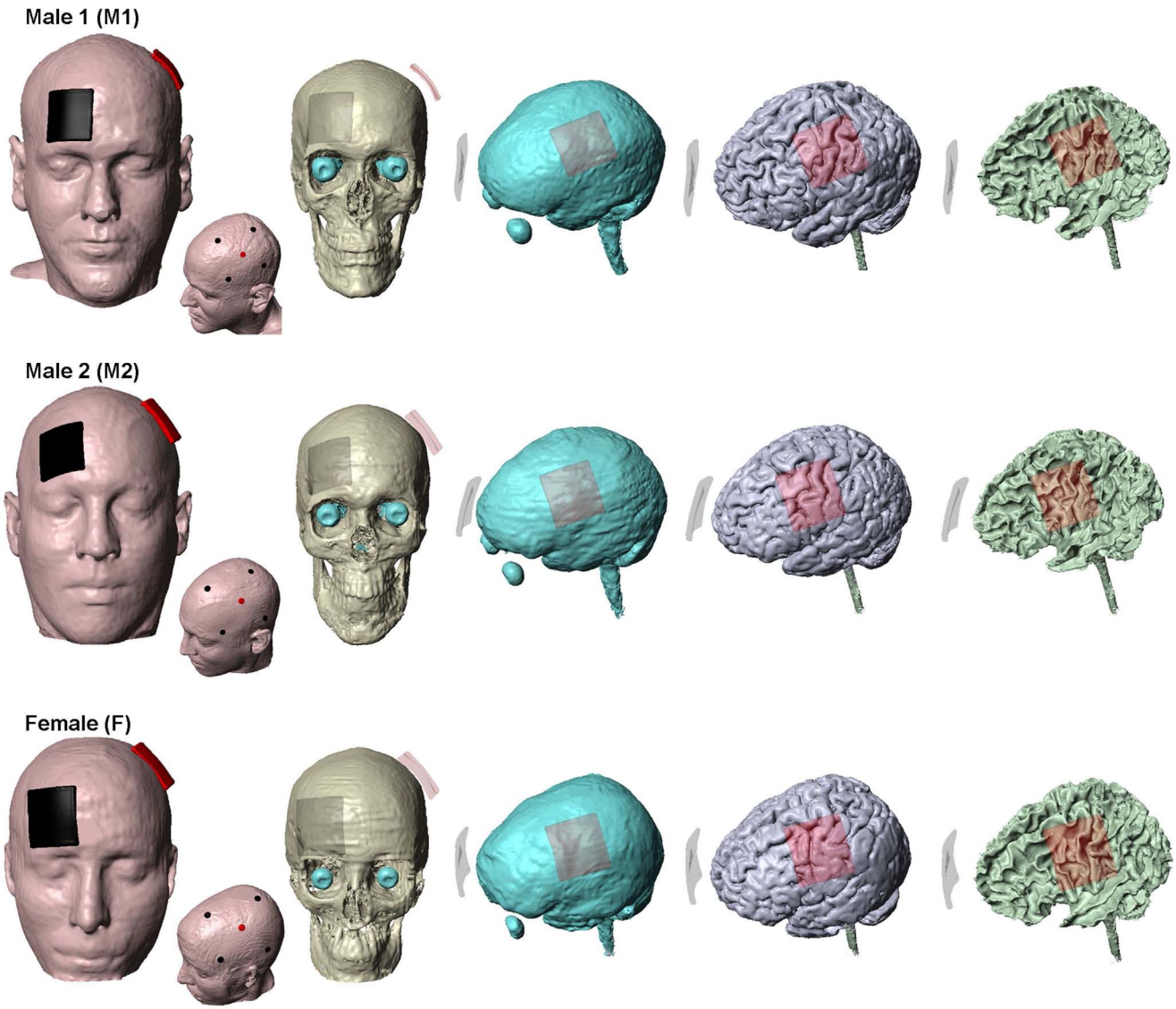

FIGURE 1 | Segmentation masks. Subject specific tissue masks of the three subjects used in the study. Skin, skull, CSF, gray matter, and white matter are shown. The traditional sponge and the 4 × 1-HD montage for each of the subjects are also shown. For the sponge montage, the anode (positive) electrode is placed over left M1 and the cathode (negative) electrode over the contralateral-supraorbita. For the 4 × 1-HD montage, the anode electrode is placed over left M1 and is surrounded by four cathode electrodes. Red: anode (positive) electrode and Black: cathode (negative) electrode.

et al., 2010). tDCS across subjects resulted in distinct predicted EF distributions in the brain. Maximal current flow was generally induced in the frontal regions *between* the electrodes across all subjects. While subject F resulted in relatively higher current flow directly *underneath* the C3 pad, the motor strip is largely spared for M1. A total current of 1 mA injected through the electrodes resulted in 0.27, 0.35, and 0.40 V/m peak cortical EF magnitudes for M1, M2, and F, respectively. Thus there is a ∼1.5-fold variation in the predicted peak induced EF values across the three anatomically normal adult subjects.

Though global individual variation in peaks and clustering is apparent by inspection, the importance of detailed and individual anatomy is further highlighted by the consideration of the zoomed regions. The zoomed motor regions have been re-plotted to 80% of the respective peak EF induced for each of the subjects to better highlight regional current flow (**Figures 2A.2,B.2,C.2**). On both macro- and micro-scales, both peak and relative current flow patterns are subject specific using the identical tDCS montage.

The boxed images showing the directional EF normal to the cortical surface distinguishes current flow direction (**Figures 2A.5,A.6,B.5,B.6,C.5,C.6**) where inward/outward direct current is expected to produce somatic depolarization/hyperpolarization (Radman et al., 2009). Here again, differences in both the peak and pattern of current flow are apparent. Finally, the sample coronal cross-section plots (taken through the motor and the frontal regions) confirm the diffuse

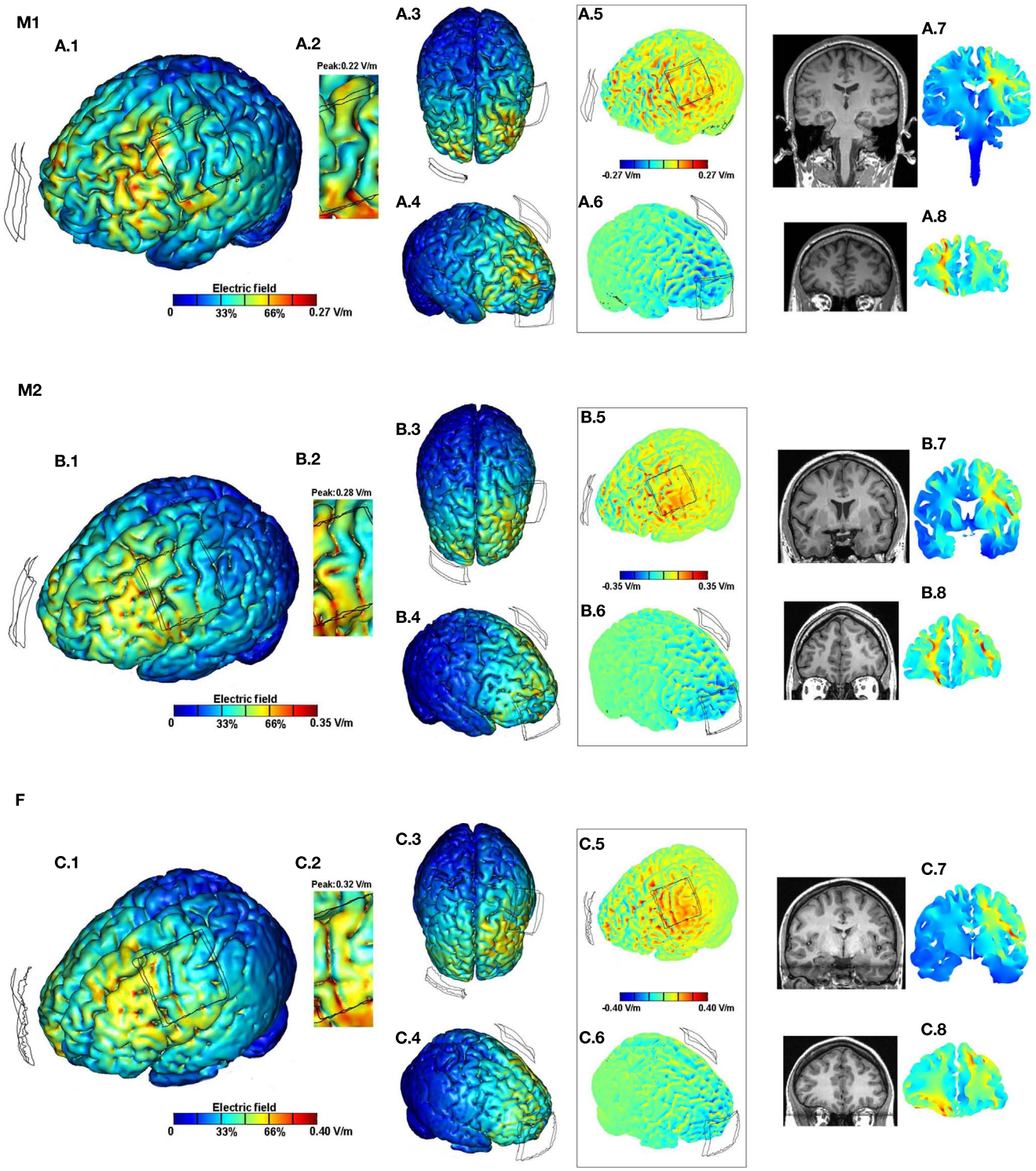

FIGURE 2 | Brain modulation across subjects (M1, M2, F) using conventional pad configuration. For each subject we plotted the induced cortical *surface* electric field (EF) magnitude: left side view **(A.1,B.1,C.1)**; top view **(A.3,B.3,C.3)**; and right side view **(A.4,B.4,C.4)**. The motor cortex is expanded and scaled to 80% of the peak induced EF for each of the subjects to better highlight current flow **(A.2,B.2,C.2)**. The boxed images show the directional plots **(A.5,A.6,B.5,B.6,C.5,C.6)**. Sample *cross-section* EF magnitude plots were taken for the frontal and the motor regions. The corresponding MRI scan collected for the subject and the cross-section plots are shown juxtaposed to each other **(A.7,A.8,B.7,B.8,C.7,C.8)**.

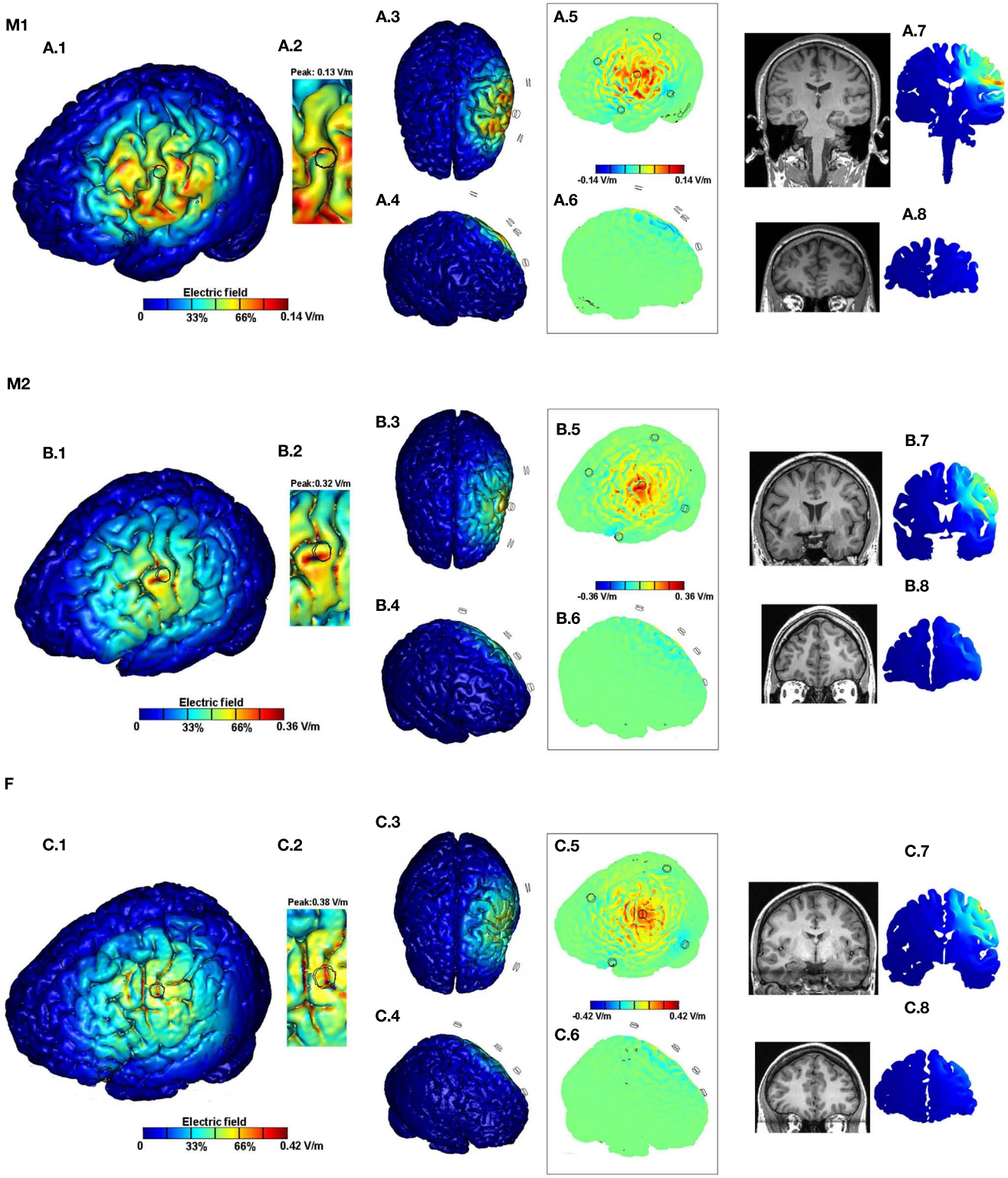

FIGURE 3 | Brain modulation across subjects (M1, M2, F) using high-definition 4 × 1 configuration. For each subject we plotted the induced cortical *surface* electric field (EF) magnitude: left side view **(A.1,B.1,C.1)**; top view **(A.3,B.3,C.3)**; and right side view **(A.4,B.4,C.4)**. The motor cortex is expanded and scaled to 90% of the peak induced EF for each of the subjects to better highlight current flow **(A.2,B.2,C.2)**. The boxed images show the directional plots **(A.5,A.6,B.5,B.6,C.5,C.6)**. Sample *cross-section* EF magnitude plots were taken for the frontal and the motor regions. The corresponding MRI scan collected for the subject and the cross-section plots are shown juxtaposed to each other **(A.7,A.8,B.7,B.8,C.7,C.8)**.

bilateral nature of current flow with the pad montage and individual variation in patterns across deep brain structures in both the frontal (**Figures 2A.8,B.8,C.8**) and motor cross-sections (**Figures 2A.7,B.7,C.7**). Subject specific local peaks are observed across the cross-sections, presumably reflecting anatomical idiosyncrasies such as proximity to ventricles.

HD STIMULATION

For all subjects, 4 × 1-ring HD-tDCS montage resulted in cortical activation circumscribed by the ring thereby leading to significant focality increases (**Figures 3A.1,B.1,C.1**). There was no significant current flow modulation in the frontal, contralateral, or on the occipital side of the brain as evidenced by the top (**Figures 3A.3,B.3,C.3**) and the right side views (**Figures 3A.4,B.4,C.4**). A total current of 1 mA injected through the electrodes resulted in 0.14, 0.36, and 0.42 V/m peak cortical EF magnitudes for M1, M2, and F, respectively. Thus there is a ∼3-fold increase in the induced EF values going from M1 to F. Inspection of global current patterns within the ring, as well as detailed consideration of the motor strip (**Figures 3A.2,B.2,C.2**; re-plotted to 90% of the respective peak EF) indicates idiosyncratic variations within the ring including difference in the rate of peak EF drop off, moving away from the center electrode. The boxed directional images confirm the unidirectional nature of the 4 × 1 montage of previous studies (Datta et al., 2008) – inward current is mostly restricted to within the cortical regions directly underneath the center electrode and the outward current is diffuse (**Figures 3A.5,A.6,B.5,B.6,C.5,C.6**). The cross-section plots confirm no modulation in the frontal regions and contralateral motor regions for all subjects (**Figures 2A.7,A.8,B.7,B.8,C.7,C.8**) with moderate variation in depth penetration across subjects.

DISCUSSION

In this study, three high-resolution anatomically accurate head models were studied to investigate the variations in current flow patterns (spatial profile/peak) due to conventional and HD montages. The observance of distinct localized clusters/hot-spots across healthy subjects reinforces the need to incorporate detailed cortical anatomy in determining brain current flow. Additionally, the variation in global patterns and the peak cortical current flow across subjects highlights the need of individual anatomy.

As expected, conventional montage was characterized by unfocal diffuse current flow while the HD montage led to field distributions restricted to within the outer ring perimeter consistent with previous modeling efforts (Datta et al., 2009; Suh et al., 2010). It follows that the diffuse current flow produced during conventional pad tDCS *aggravates* individual differences. tDCS resulted in several peak clusters spanning the frontal lobe including cortical and deeper structures. Though for these three subjects, the peak EF varied more for 4 × 1-ring HD-tDCS compared to conventional tDCS (3× vs. 1.5×), the peak EF remained confined to the cortex under the center electrodes and in no case did current invade brain regions substantially outside the ring. The maximum EF on localized hotspots at the bottom of the sulci may have contributed to a bigger variation for the 4 × 1 montage. Furthermore, it has been previously reported that 2 mA – 4 × 1 at 3 cm separation corresponds to comparable EFs at 1 mA sponge stimulation. The results of this study show that at 6 cm separation – 1 mA, 4 × 1 may lead to comparable or even higher EFs in comparison to sponges.

The viability of HD stimulation was first shown in the Minhas et al. (2010) study by using appropriate hardware (electrode material, gel, and electrode adapters). Since then several clinical studies have been initiated in healthy and diseased subjects to explore the efficacy of HD-tDCS stimulation. 4 × 1-Ring HD-tDCS has been shown to be efficacious for experimental pain (Borckardt et al., 2012) and in Transcranial Magnetic Stimulation – Motor Evoked Potential (Caparelli-Daquer et al., 2012) studies. While these initial studies additionally address the viability of this technique and its safety/tolerability profile, they do not directly address whether a more targeted therapy equates to a more beneficial outcome. Naturally, future research will have to adjudicate whether a focal therapy will lead to similar, worse, or better outcomes than traditional sponge electrode montages.

It is not tractable to explicitly compare brain current flow across hundreds of heads using currently available computational resources and software (as usually done by MR analysis to study inter-individual anatomical differences; Gur et al., 2002). Rather the goal on this study was to access the degree of potential changes expected even across comparable age healthy adults. One may venture into general dose guidelines, such as the role of head-size, gender, or if the order of EF sensitivity will be maintained across montages, but with this limited set of data, this is speculative. Thus further automation of the modeling process remains critical for economical and broad dissemination. Inferences are further complicated, as there is likely no simple (one to one) relationship between current in any given region and behavioral/clinical outcomes. What is clear is that changes in peak brain EF ∼3-fold can be expected and potentially more if more diverse adult healthy individuals are considered. If one assumes that roughly doubling or more stimulation intensity is functionally meaningful (as indeed shown in clinical studies), then these results suggest difference in current flow due to individual differences is a significant source of variability in tDCS.

What steps can be taken to normalize dose? In regards to peak EF, the simplest approach is to "scale" applied current across subjects. For example, stimulation using the M1-SO montage in subject M1 using 1.5 mA produces comparable peak EF as stimulation in subject F. More generally, if the model predicted × times higher current in the target region for a head than for a baseline "efficacious" head, a simple way to "normalize" dose would be reduce the total injected current by a factor of ×. A variation of up to ∼3.7-fold in peak EF was predicted in a study comparing an idealized skull defect to a healthy adult head (Datta et al., 2010). Likewise, higher variation is expected going from pediatric to elderly population. Normalizing dose across a diverse population thus requires subject specific MRI-derived models using available gross anatomical features (such a system is in development at City College New York: CCNY-Dose System). However, normalizing for variation in current flow pattern is more complex and cannot be addressed by simply changing applied currents or adjusting pad placement. In this regard, montages such as the 4 × 1-ring are compelling because they, at a minimum, at least constrain which brain regions are potentially modulated.

Though we expect the main conclusions of this study are robust, the accuracy of any FEM model is limited not only by the precise representation of anatomy but also by material properties (including anisotropy). Preservation of 1 mm resolution throughout the modeling workflow led us to accurately capture individual specific cortical folds/contours, skull architecture, continuous CSF layer – which consequently led to the individual differences, reported here. Improving the precision of the model by incorporating DTI conductivities in the anisotropic (white matter and the skull) regions as well as to establish reliable DC conductivities for the remaining isotropic regions is needed. More importantly, directly validating the patient-specific modeling predictions by their individual functional effects by applying DC stimulation (e.g., MEP changes following motor cortex stimulation) in a clinical study is ideally required.

Keeping with the ultimate goal of optimizing tDCS therapy and reducing variability, consideration of current flow patterns remains paramount for design of montages and interpretation of patient-specific results – thus the ability to individualize therapy must be leveraged. The predictions of this study are the first step to explore reported inter-individual differences via computer modeling. The data suggest that individualized modeling may require consideration in determining tDCS efficacy. Future work will need to determine whether subject specific dosing based on modeling is meaningfully beneficial for tDCS outcomes or if currently used fixed-dose approaches are sufficient.

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Transcutaneous spinal direct current stimulation

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In the past 10 years renewed interest has centered on non-invasive transcutaneous weak direct currents applied over the scalp to modulate cortical excitability ("brain polarization" or transcranial direct current stimulation, tDCS). Extensive literature shows that tDCS induces marked changes in cortical excitability that outlast stimulation. Aiming at developing a new, non-invasive, approach to spinal cord neuromodulation we assessed the after-effects of thoracic transcutaneous spinal DC stimulation (tsDCS) on somatosensory potentials (SEPs) evoked in healthy subjects by posterior tibial nerve (PTN) stimulation. Our findings showed that thoracic anodal tsDCS depresses the cervico-medullary PTN-SEP component (P30) without eliciting adverse effects. tsDCS also modulates post-activation H-reflex dynamics. Later works further confirmed that transcutaneous electric fields modulate spinal cord function. Subsequent studies in our laboratory showed that tsDCS modulates the flexion reflex in the human lower limb. Besides influencing the laser evoked potentials (LEPs), tsDCS increases pain tolerance in healthy subjects. Hence, though the underlying mechanisms remain speculative, tsDCS modulates activity in lemniscal, spinothalamic, and segmental motor systems. Here we review currently available experimental evidence that non-invasive spinal cord stimulation (SCS) influences spinal function in humans and argue that, by focally modulating spinal excitability, tsDCS could provide a novel therapeutic tool complementary to drugs and invasive SCS in managing various pathologic conditions, including pain.

Keywords: transcranial direct current stimulation, transcutaneous spinal direct current stimulation, spinal cord, pain

INTRODUCTION

In the past two decades growing interest has centered on non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Extensive literature shows that tDCS can modulate activity in specific cerebral cortex regions by inducing marked changes in cortical excitability that outlast stimulation (Nitsche et al., 2003a; Priori, 2003; Paulus, 2004; Priori et al., 2009; Stagg and Nitsche, 2011). Thanks to its low costs, acceptable safety data and potential use in outpatients, tDCS is increasingly being evaluated in proof-of-principle and pivotal clinical trials in widely ranging neurological and psychiatric disorders (Murphy et al., 2009; Nitsche et al., 2009; Baker et al., 2010; O'connell et al., 2011; Schlaug et al., 2011). Numerous studies have addressed the physiological effects induced by tDCS on the cerebral cortex and evidence comes from stimulation applied to the primary motor cortex (M1; to review Stagg and Nitsche, 2011). tDCS can modulate cortical excitability and neuronal firing rates. Direct current stimulation changes the resting neuronal membrane potential in the cortex layers (Bindman et al., 1964; Purpura and McMurtry, 1965). Depending on the duration and strength of polarization, these changes can persist after stimulation offset. Long-lasting effects after brain polarization probably arise through synaptic changes via long-term potentiation (LTP) and depression (LTD; Liebetanz et al., 2002; Nitsche et al., 2003a) as well as non-synaptic mechanisms (Ardolino et al., 2005).

Surprisingly, rediscovering the use of direct currents on the brain has not yet prompted a similar effort to explore the possibility of using non-invasive, transcutaneous, direct current stimulation to modulate spinal cord function. Having a technique for modulating spinal function is important for various reasons. First, several neurologic diseases and syndromes arise from an acquired or congenital selective spinal cord dysfunction. Given that the brain and spinal cord interact through several projections and that DC stimulation over the spine may modulate different supraspinal activities, transcutaneous spinal DC stimulation (tsDCS) has numerous clinical applications. Finally, invasive electrical spinal cord stimulation (SCS) has been used for more than 30 years to treat a variety of pain syndromes. Traditionally used for persisting leg pain after lumbar spinal surgery, SCS has been applied successfully in the treatment of angina pectoris, ischemic pain in the extremity and complex regional pain syndromes (Grabow et al., 2003; Mailis-Gagnon et al., 2004; Ubbink and Vermeulen, 2005; Frey et al., 2009). The aim of this paper is to review studies on the use of tsDCS in humans focusing on the technique's physiological effects and potential clinical applications. The first step in conducting the review involved a selective literature search for papers published from 1990 to March 2012.

We used the PUBMED of the National Library of Medicine database. Our key search terms were "direct current stimulation" or "tsDCS" or "polarization" and "spinal cord" with the limitation that studies were written in English.

EFFECTS OF tsDCS ON SPINAL TRACTS

LEMNISCAL TRACT

To investigate whether transcutaneous direct currents can interfere with ascending somatosensory pathways in the human spinal cord, in a study from our group we evaluated the after-effects induced by anodal and cathodal tsDCS on somatosensory potentials (SEPs) evoked by stimulating the posterior tibial nerves (PTN; Cogiamanian et al., 2008). We applied current at a density of 0.071 mA/cm^2 and delivered a total charge of 63.9 mC/cm^2 (2.5 mA for 15 min, electrode area 35 cm^2) with the active electrode located on the thoracic spinal cord (over the spinous process of the tenth thoracic vertebra) and the reference above the right shoulder. Anodal tsDCS selectively reduced the amplitude of the cervico-medullary component (P30) of PTN-SEPs for at least 20 min after stimulation offset. Conversely cathodal tsDCS left P30 almost unchanged in amplitude.

By analogy with the effects of DC currents on peripheral nerve axons, we hypothesized that anodal currents hyperpolarize sensory axons running in the posterior columns of the spinal cord ultimately leading to an "anodal block" (Bhadra and Kilgore, 2004). Interestingly whereas anodal tsDCS decreased amplitudes it left latencies unchanged. This finding agrees with the observation that also at peripheral nerve level anodal polarization decreases the size of the motor responses, but not the latency (Priori et al., 2005). Anodal tsDCS could fail to induce latency changes because it blocks impulse conduction in some axons, leaving conduction in the remaining axons unaltered. Our data were indirectly confirmed in a subsequent study by Aguilar et al. (2011) in anesthetized rats. These authors investigated how direct current spinal stimulation delivered at thoracic level influences spontaneous activity and SEPs in the gracile nucleus and primary somatosensory cortex. They used a different stimulation setup with one electrode placed on the thoracic spinal cord over the exposed dura mater, and the second under the skin in the anterior abdominal area aiming to maximize the current focus in the spinal cord below the dorsal electrode. Anodal spinal direct current stimulation (sDCS) increased spontaneous activity in the gracile nucleus while decreasing its local field potentials responses to somatosensory stimuli, and cathodal sDCS did the opposite. This inverse relationship between gracile spontaneous activity and local field potentials, the equivalent of SEPs at brainstem level (P30), depended on several mechanisms including pre-synaptic inhibition, synaptic depression, and shunting inhibition (Aguilar et al., 2011).

SPINOTHALAMIC TRACT

Given this basic ability of tsDCS to modulate conduction in the lemniscal pathway, Truini et al. (2011) sought further information by evaluating the effects of thoracic tsDCS (2.5 mA, 20 min) on the spino-thalamic tract. To do so, they investigated the after-effects of anodal and cathodal tsDCS delivered on the skin overlying the thoracic spinal cord on foot and perioral laser evoked potentials (LEPs) in a group of healthy subjects. Peripheral laser stimulation selectively activates Aδ and C mechano-thermal nociceptors (Treede et al., 1995), and evokes scalp potentials related to small myelinated (Aδ) fibers (Romaniello et al., 2003). Using an electrode set-up (active electrode on the thoracic spinal cord on the skin over the thoracic spinous process of the tenth thoracic vertebra and the reference above the right shoulder) as well as a stimulation protocol (2.5 mA, 20 min) similar to those we used in our earlier study Cogiamanian et al. (2008) and Truini et al. (2010) showed that anodal tsDCS reduced LEPs amplitude after foot stimulation whereas cathodal polarity induced a slight non-significant attenuation over time. Neither anodal nor cathodal tsDCS changed LEP variables after perioral stimulation suggesting that the DC-induced changes took place at spinal level. In an additional experiment to better understand the behavioral significance of these findings on LEPs the same investigators tested the effects of thoracic tsDCS on the foot-cold-pressor test, a pain model that has been widely used in human pain research. The foot-cold-pressor test analysis disclosed higher pain tolerance during anodal than during cathodal tsDCS. Conversely, no significant difference was found in the pain threshold between the two polarity conditions. The lack of tsDCS effects on LEPs and cold-pressor test thresholds was related to a poor sensitivity of these variables as minimal afferent input could be sufficient to maintain them normal (Truini et al., 2010).

EFFECTS OF tsDCS ON SPINAL REFLEXES

Besides its ability to modulate the progression of sensory or nociceptive inputs along the spinal cord tsDCS could also modulate spinal cord activity at segmental level. Two studies evaluated how transcutaneously applied direct currents influence spinal circuitries. In the first, Winkler et al. (2010) focused on tsDCS-induced changes in H-reflex size and post-activation H-reflex depression (or homosynaptic depression) namely, reduced H-reflex amplitude within 8–12 s after Ia fibers afferent activation. Earlier evidence already showed that reduced synaptic efficacy is related to decreased neurotransmitter release and exclusively affects the previously activated Ia fiber-motoneuron synapse with no effects due to supraspinal influences (Grey et al., 2008). tsDCS was applied using a pair of self-adhesive electrodes (40 cm^2), the active one placed about 2 cm left paravertebrally to the 11th thoracic vertebra and the other in the left infraclavicular region. Direct current was administered for 15 min at an intensity of 2.5 mA, resulting in a current density of 0.063 mA/cm^2 and a total delivered charge of 0.056 C/cm^2.

General H-reflex excitability, measured with the Hmax/Mmax ratio, remained statistically unchanged after stimulation but anodal tsDCS induced a long-lasting decrease in H-reflex post-activation depression and cathodal tsDCS increased it. The investigators suggest that stimulation modulated efficiency in the Ia fiber-motoneuron synapse without influencing excitability in the alpha-motoneuron (Winkler et al., 2010).

In our laboratory we evaluated changes induced by thoracic tsDCS on the lower limb flexion reflex (LL-Fr) in 11 healthy subjects (Cogiamanian et al., 2011). The Fr is a polysynaptic spinal reflex elicited by electrical stimulation applied to a sensory nerve and is a reliable and widely investigated neurophysiologic tool to assess the efficacy of analgesic therapies (Cruccu et al., 2004). The

Fr comprises an early response, the RII reflex (RIIr) and a late response, the RIII reflex (RIIIr). Various studies have shown that the RIIr is a non-nociceptive Aβ fiber mediated response, whereas the RIIIr is a high-threshold nociceptive Aδ fiber mediated reflex. The RIIIr threshold corresponds to the pain threshold and the size of the reflex is related to the pain perception level (Sandrini et al., 2005). Subjects underwent anodal tsDCS (2 mA, 15 min) and sham stimulation in a cross-over design with active (anodal) electrodes placed over the spinal process of the tenth thoracic vertebra and the cathode (reference) above the right shoulder. Thoracic anodal tsDCS induced a long-lasting Fr depression and reduced the RIII area by 27%. Both changes lasted for at least 30 min after stimulation offset. Because stimulation left H reflex variables unchanged we exclude the possibility that tsDCS inhibits the nociceptive reflex by modulating excitability in the mono-oligosynaptic segmental reflex pathway. These data along with the changes induced by tsDCS on foot-LEPs (Truini et al., 2011) reflect an attenuation of spinal processing of nociceptive inputs. Even though the exact mechanism through which tsDCS acts remains elusive it seems unrelated to the "gate theory of pain" advocated by Melzack and Wall (1965) to explain the analgesic effects of invasive epidural SCS. This theory proposed that the position of the "gate" depends upon the degree of large (non-painful) or small (painful) nerve fiber firing. When stimulation activates faster large fibers (as does SCS) the gate closes so that no impulses can pass through, thus eliminating or reducing pain. Conversely, when it predominantly activates small nerve fibers, pain messages can be transmitted. Placing the active anodal electrode on the thoracic spine in tsDCS experiments makes it unlikely that tsDCS directly activates Aβ fibers (closing of the gate) ascending from the foot. Equally important, a fundamental concept of SCS is that the analgesic effects rely on a sustained and strictly homotopic input that the subject must perceive on the projection territory (Oakley and Prager, 2002). Ample evidence shows that tsDCS induces occasional, transient, and short-lasting tingling and burning sensations just below the stimulating electrodes and that DCS strength remains below the conscious sensory threshold throughout the experimental sessions (Cogiamanian et al., 2008, 2011; Truini et al., 2011).

Similarly, we can exclude the possibility that tsDSC induces its modulatory effects by a specifically activating diffuse noxious inhibitory controls (DNIC). In our experiments (Cogiamanian et al., 2011) after anodal skin stimulation away from the spinal cord producing the same itching sensation as the original experiment, LL-Fr variables remained unchanged. In addition, Truini et al. (2011) showed that thoracic tsDCS had no effect on LEPs evoked by perioral stimulation (exceeding the tsDCS stimulation level).

From current knowledge we therefore hypothesize that tsDCS acts at spinal level. In humans nociception is mediated by a complex interneuronal network that integrates peripheral inputs, multisensory feedback, and supraspinal descending projections. Animal models of experimental mononeuropathy show that, in response to sciatic nerve lesions, multireceptive, wide dynamic range (WDR) neurons in the deeper lamina of the rat dorsal horn increase their spontaneous firing rates and exhibit after-discharge behavior that is attenuated by SCS (Dubuisson, 1989). tsDCS could interfere with the ascending nociceptive spinal pathway by reducing the "gain" in spinal nociceptive information transmission by modulating activity in the spinal interneuronal network. tsDCS could mediate this effect by directly activating segmental interneurons (i.e., WDR neurons) or by modulating dorsal column transmission via collaterals to dorsal horns. Alternatively, tsDCS could activate supraspinal loops, relayed by the brainstem or thalamocortical systems, thereby providing both ascending and descending inhibition.

SAFETY CONSIDERATIONS

Even though tDCS and tsDCS are non-invasive techniques for neuromodulation and are commonly considered safe, caution is required. The use of tDCS in therapeutic protocols to date has not resulted in severe adverse effects, but some safety issues remain controversial. In an early study, Nitsche et al. (2003b) suggested that the appropriate variables for determining safety limits for tDCS should be current density (CD, mA/cm^2) and total charge (TC, C/cm^2). Data from the literature suggests that tissue damage occurs at a TC of 216 C/cm^2 (Yuen et al., 1981) and that a CD below 25 mA/cm^2 (McCreery et al., 1990) induces no tissue damage. Notably, the stimulation variables commonly used are a thousand-fold lower than these limits. When it begins and after it ends, tDCS often elicits short-lasting tingling sensations, rarely accompanied by redness under the electrode sites.

Safety data for tsDCS are scanty. No spinal-specific adverse events have been reported after tsDCS and we excluded direct harmful effects of tsDCS over spinal cord by assaying serum neuron specific enolase (NSE) before and immediately after stimulation offset (Cogiamanian et al., 2008). Although the stimulation variables that have been used in tsDCS protocols were comparable with those used in tDCS studies, we cannot exclude harmful effects due to a high local current density related, for instance, to current flow via the spinal foramina.

For future studies, patients undergoing tsDCS should be carefully monitored for adverse effects with conventional magnetic resonance imaging (MRI) or spectroscopy, because safety issues related to tsDCS may emerge only with larger studies or using novel stimulation protocols with repetitive daily sessions.

CONCLUSION

The few papers published over the past 5 years we review here provide ample evidence that tsDCS induces changes in spinal cord function. The physiological mechanisms underlying these changes need further investigation. Because, unlike the brain, no methodology is available for non-invasive spinal neuromodulation, the possibility of influencing conduction along the ascending spinal pathways in humans is interesting, especially for clinical purposes.

Although its basic ability to modulate several neurophysiologic variables does not guarantee that tsDCS is effective as a clinical technique, because it induces no adverse effects, is simple and non-invasive, the findings from this review open the way to new approaches using non-invasive tsDCS for treating disorders that are presently managed with invasive methods. The widespread use of high-frequency epidural electrical stimulation to treat various chronic pain syndromes has prompted research to investigate whether tsDCS could be used to modulate nociception with a

new non-invasive approach. tsDCS also promises to be useful in neurorehabilitation, especially in treating spasticity.

A major drawback that limits tsDCS for clinical use is that DC applied to single brain areas or to the spine induce after-effects that persist only for several minutes to several hours. Some help in prolonging the beneficial effects induced by tsDCS could come from optimizing stimulation protocols and devices. Various therapeutic protocols can be used to prolong the neuromodulatory effect of tsDCS. For example, patients can undergo repetitive sessions (i.e., daily sessions for more than two consecutive days) increasing the total charge administered. Portable tsDCS devices that outpatients can be trained to use daily or in repeated sessions are already available.

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