Brain Stimulation 8 (2015) 1108–1115

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Use of Computational Modeling to Inform tDCS Electrode Montages for the Promotion of Language Recovery in Post-stroke Aphasia

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ARTICLE INFO

Article history:
Received 16 March 2015
Received in revised form
22 June 2015
Accepted 24 June 2015
Available online 18 July 2015

Keywords:
Aphasia
tDCS
Modeling
Language rehabilitation
Neuromodulation

ABSTRACT

Background: Although pilot trials of transcranial direct current stimulation (tDCS) in aphasia are encouraging, protocol optimization is needed. Notably, it has not yet been clarified which of the varied electrode montages investigated is the most effective in enhancing language recovery.
Objective: To consider and contrast the predicted brain current flow patterns (electric field distribution) produced by varied 1×1 tDCS (1 anode, 1 cathode, 5 × 7 cm pad electrodes) montages used in aphasia clinical trials.
Methods: A finite element model of the head of a single left frontal stroke patient was developed in order to study the pattern of the cortical EF magnitude and inward/outward radial EF under five different electrode montages: Anodal-tDCS (A-tDCS) over the left Wernicke's area (Montage A) and over the left Broca's area (Montage B); Cathodal tDCS (C-tDCS) over the right homologue of Wernicke's area (Montage C), and of Broca's area (Montage D), where for all montages A-D the "return" electrode was placed over the supraorbital contralateral forehead; bilateral stimulation with A-tDCS over the left Broca's and CtDCS over the right Broca's homologue (Montage E).
Results: In all cases, the "return" electrode over the contralesional supraorbital forehead was not inert and influenced the current path through the entire brain. Montage B, although similar to montage D in focusing the current in the perilesional area, exerted the greatest effect over the left perilesional cortex, which was even stronger in montage E.
Conclusions: The position and influence of both electrodes must be considered in the design and interpretation of tDCS clinical trials for aphasia.

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Introduction

Aphasia is a cognitive language disorder that affects over a million people who have sustained a left-hemisphere stroke. Although traditional behavioral treatment in the form of speech-language therapy has been shown to improve aphasic disorders in some studies [1], many people with aphasia post-stroke experience lifelong language and communication deficits [2]. In the past decade, researchers have investigated the use of noninvasive neuromodulation techniques and, in particular, transcranial direct current stimulation (tDCS) to promote language recovery in post-stroke aphasia [3]. While the first published study [4] that documented tDCS use for aphasia rehabilitation did not include a behavioral treatment protocol, studies since then have combined tDCS with speech-language therapy [5–21]. These initial studies generally included behavioral treatment for anomia and

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http://dx.doi.org/10.1016/j.brs.2015.06.018
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implemented noun retrieval as the outcome measure; more recent studies have included additional behavioral treatments for the recovery of verbs [5,7,13], articulation [9] and discourse productivity [6,8]. However, although the behavioral treatment component has progressed from its initial focus on word retrieval, the electrode montages implemented for the administration of tDCS have remained consistent over time. These involve electrodes in a 1×1 configuration with one electrode placed over the ipsilesional or contralesional cortex and the other electrode placed over the contralateral supraorbital area or in an extracephalic position (i.e. the contralateral shoulder [e.g. Ref. 21]). In studies of aphasia rehabilitation, many researchers have placed the anode over the left Broca's or Wernicke's area (conventionally located using the 10-20 EEG system method) delivering excitatory current, and the cathode, referred to as the "return" electrode, on the contralateral supraorbital region of the forehead [5–9,11,13–16,20]. The rational for this placement was generally supporting the notion that the reactivation of the perilesional areas of the left hemisphere usually leads to a better language outcome than the involvement of homotopic contralateral regions [22,23,24, but see 25]. Consistent with this assumption, some evidence has suggested that the right hemisphere activity may limit language recovery if its processing is dysfunctional, or if transcallosal projections from the right inhibit the left language areas [26,27]. Accordingly, some tDCS language studies have used a different montage placing the cathode over the right Broca's or Wernicke's homologue area in order to deliver inhibitory current, and in this case the anode is the "return" electrode, placed over the left supraorbital region [10,12,15,17–20]. The rationale for using this montage was that inhibitory stimulation of intact contralesional cortical areas may facilitate increased recruitment of perilesional regions of the left hemisphere into reorganized language networks by diminishing the impact of transcallosal inhibitory inputs to those areas [26,27]. More recently, bilateral bipolar balanced tDCS [28], with simultaneous anodic ipsilesional and cathodic contralesional stimulation over specific cortical brain regions is beginning to be considered as an effective manner for administration of tDCS. The rationale for implementing bilateral tDCS was based on the assumption that simultaneously upregulating excitability of the intact portion of the ipsilesional hemisphere through anodic stimulation while at the same time downregulating excitability of the contralesional hemisphere through cathodic stimulation should lead to the greatest recovery. This has been demonstrated in the motor domain by Lindenberg et al. [29] but has also recently been implemented in aphasia tDCS rehabilitation-research studies [30–34]. However, a major misconception in most of the aphasia unilateral bipolar 1×1 tDCS studies was that the focus and interest has been on the active electrode and researchers have neglected the role of the "return" electrode, assuming that, since the prefrontal cortex is not critically involved in language processing, the supraorbital electrode would be irrelevant with respect to the underlying area. When defining the "dose" of tDCS, electrode montage (size of electrode and location), duration, and intensity in mA, are all important factors. The montage involves two electrodes and the location of these two electrodes, not just the conventionally described "active" electrode, dictates where the current goes in the brain [35]. Understanding the relevance of all of the aspects of tDCS "dose" which affect current flow and controlling the current flow is critical in determining behavioral and clinical outcomes. Specifically, the position of the electrodes governs current flow and hence the distribution of induced electric fields in the brain. These induced cortical currents modulate neuronal excitability for DC stimulation and, in turn, determine behavioral and clinical outcomes [36]. The return electrode can contribute directly to physiological effects when placed over the cranium as well, and will affect electrical field orientation which is critical for the efficacy and direction of the current [36,37].

The importance of the current density and the direction of current flow in relation to different electrode montages on healthy brains has already been investigated by different studies [38,39]. With regard to the language domain, only one study by Datta et al. [40] documented current flow pattern among different montages in a patient with aphasia. In that study, unilateral bipolar 1x1 tDCS was administered. The subject was treated with anodal tDCS applied over the left Broca's area with the cathode placed on the right shoulder. Finite element computational modeling was used retrospectively to describe the current density and direction of current flow while the electrodes were in this position. In addition, in order to consider current density direction given different montages, models were also computed with the cathode over the right mastoid and the cathode over the right frontal orbital region, for comparison purposes. A fourth model was computed implementing what the authors described as a "mirror montage" where the anode was placed over the right Broca's area and the cathode on the left shoulder. In each of these four montage configurations, differences were reported in terms of current density and direction of current flow. This first published report by Datta et al. [40] suggests that current density and direction of current flow are dependent upon the implemented montage, which involves both electrodes. The three models with the anode consistently over Broca's area and the cathode on the right shoulder, mastoid, or supraorbital region, respectively, show that current density and direction of current differ among models of these three montages while the "active" anode remains consistent over Broca's area in all three models. Yet, even after this 2011 report, most aphasia tDCS studies have not considered both electrodes as active and have reported one electrode as the "return" electrode assuming that it is inert and does not influence the current flow, when indeed it does.

The aim of this paper was to retrospectively consider previously published research that implemented tDCS and behavioral treatment for the recovery of language in post-stroke aphasia in relation to tDCS electrical field (EF) current density and current direction (radial EF) as determined by computational modeling techniques. As previously stated, current density EF magnitude and radial EF were observed to predict neuronal modulation in transcranial stimulation modeling [38,39]. For weak static fields, neuronal excitability changes monotonically with strength of EF magnitude [41–48]. Different from Datta et al.'s study [40], our aim was to directly compare the most frequent electrode montages used in the tDCS aphasia literature in order to investigate the corresponding brain current flow patterns. The development of high-resolution computational models is a method that will help inform researchers prospectively design studies that include optimal electrode montages for brain modulations. While individualized modeling for each specific participant may be informative [40], it is prohibitive due to a variety of factors including technological capacity, intensity of labor, and cost. Considering the current flow (EF) among the five most common electrode montages used presently in tDCS aphasia studies, will help inform researchers regarding the degree and direction of the current throughout the brain during administration of tDCS and the relevant importance of both the anode and the cathode when implementing this technique for the promotion of language recovery in post-stroke aphasia.

Materials and methods

MRI-derived finite element modeling

A finite element model of the head of an individual who sustained a single left hemisphere frontal stroke (see Fig. 1) was

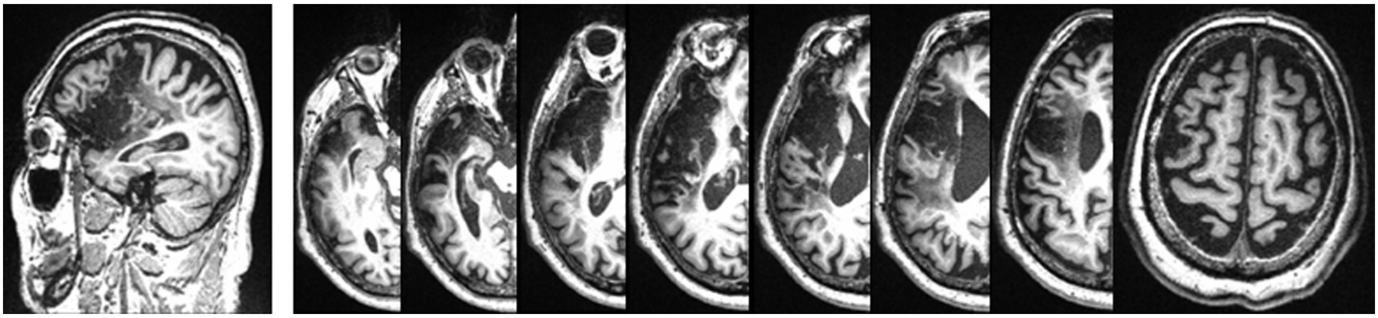

Figure 1. MR's description. Lesion is localized in the superior portion of the middle frontal gyrus (BA 6–4), in the inferior frontal gyrus (BA44) affecting the underlying white matter and in the anterior insula. The lesion also affected the anterior temporal lobe and, subcortically, the extreme, external and internal capsule, the putamen, the globus pallidus and the claustrum.

obtained in order to study the diffusion of the electric field into the brain while administering tDCS via different electrode montages.

The process for choosing the MRI to be modeled included three independent raters who reviewed four different MRIs. All MRIs were from patients who had sustained a single lesion in the frontal cortex. Each rater had experience reviewing MRIs of brains post-stroke. The raters were asked to rank order the MRIs to use for the modeling and they were instructed to choose the MRI that best exhibited a single anterior lesion in the left frontal region (i.e. Broca's area) since this is the most frequently affected area in left-stroke patients [49]. Each independent rater rank ordered the four MRIs and all three raters chose as number one the MRI that was decided to be used for the modeling described in this paper. It was agreed by each independent rater that the MRI chosen was the best representation that exhibited a single left hemispheric stroke in the anterior frontal region corresponding to Broca's area.

The model was generated from a 3T MRI scan that had an isotropic 1 mm^3 resolution. The MRI was segmented by ScanIP software (Simpleware, Exeter, UK) to turn each voxel into a conductor volume with the conductive isotropic average features of the pertinent head tissue. In this way, we obtained seven different electric compartments: air (1×10^{-4} S/m), bone (1×10^{-2} S/m), skin (0.465 S/m), cerebrospinal fluid (CSF, 1.65 S/m), grey matter (0.276 S/m), white matter (0.126 S/m) and the lesion, electrically classified like the CSF as shown in several previous studies [35–43]. The rectangular electrodes with their proper 35 cm^2 sponges were rendered as CAD files and imported into ScanCAD (Simpleware Ltd, Exeter, UK) for manual positioning over the scalp of the 3D model. To deliver current through sponges into the brain during a transcranial electrical stimulation (tES) experiment, the sponges are soaked in saline for tDCS stimulation. Therefore we assigned the sponges the conductivity of saline (1.4 S/m). All masks were imported in ScanIP (Simpleware Ltd, Exeter, UK) to generate a mesh consisting of more than 10,000,000 tetrahedral elements and more than 15 million degrees of freedom. Then the mesh was imported in COMSOL Multiphysics 4.3 (Burlington, MA) to solve the equations related to the diffusion of the electric field into this finite elements space.

Model solutions

To represent the conventional montages used in aphasia (see Table 1), we modeled five different montages using 7×5 cm^2 sponge electrodes over the scalp, electrode location determined by the International 10-20 System. The position of the electrodes in Montages A, B, C, D, and E were:

Montage A) Anodic stimulation over Wernicke's area: "active" electrode on CP5 and cathode (return electrode) over the contralateral supraorbital area.

Montage B) Anodic stimulation over Broca's area: "active" electrode placed on F5 and cathode (return electrode) over the contralateral supraorbital area.

Montage C) Cathodic stimulation over the right homologue of Wernicke's area: "active" electrode placed on CP6 and anode (return electrode) over the contralateral supraorbital area.

Montage D) Cathodic stimulation over the right homologue of Broca's area: "active" electrode on F6 and anode (return electrode) over the contralateral supraorbital area.

Montage E) Bilateral stimulation with anodic stimulation over Broca's area and cathodic stimulation over the right homologue of Broca's area.

The Laplace equation $\nabla \cdot (\sigma \nabla V) = 0$ was solved using the following boundary conditions: current densities corresponding to 1 mA total current, having a flow normally applied to the scalp and ground applied to the surface of the cathode electrode. The finite element model was implemented by COMSOL Multiphysics 4.3, using a linear system solver of conjugate gradients with a relative tolerance of 1×10^{-14} [40].

Results

EF distribution analysis

Results showed that all the conventional montages A, B, C, and D deliver a current flow pattern whose field widely involved both hemispheres. Therefore, the position of the orbifrontal "return" electrode, whether over the left or the right side, significantly affected brain current flow with substantial EFs in the cortex under the electrode and between the electrodes in the fronto-temporal regions for montages A and C and in the frontal regions for montages B and D. The radial component of the EF reveals the same general trend: incoming current in the left hemisphere and outgoing current from the right hemisphere (see Fig. 2).

However, the comparison of cortical current flow prediction among the different montages reveals some crucial differences. Firstly, the distance between the electrodes significantly affected the EF distribution. Indeed, in montages A and C, due to the greater distance between the electrodes, the EF was more diffuse throughout the brain. Different from this, for montages B and D, where the electrodes were closer in proximity, the EF was concentrated in the frontal regions with manifest changes both in the left perilesional area and contralateral frontal cortex. The comparison between montage B and D revealed that the current flow pattern was very similar whether the anodic current was delivered over the left Broca's area (montage B) or the cathodic stimulation was applied over the right homologue of Broca's area (montage D), when in both cases, the "return" electrode was placed

Table 1
tDCS studies in aphasia recovery by montage.

Studies	Type of aphasia	Modeled montage	Targeted area and reference electrode	Intensity/Duration	Concomitant speech therapy	Effects
Fiori et al. (2011) [14]	3 nonfluent	Montage A	A/S LST cortex supraorbital RF	1 mA, 20 min, 5 sessions	Novel word training, verification task, and noun naming	AtDCS improved accuracy and reduced reaction times for noun naming
Fridrikson et al. (2011) [16]	8 fluent	Montage A	A/S L posterior cortex supraorbital RF	1 mA, 20 min, 5 sessions	Spoken N picture word matching	AtDCS reduced reaction time in N naming trained items
Fiori et al. (2013) [13]	7 nonfluent	Montage A	A/S LST cortex supraorbital RF	1 mA, 20 min, 5 sessions	N and V Naming	AtDCS improved N and V naming, N > V
		Montage B	A/S LIF cortex supraorbital RF	1 mA, 20 min, 5 sessions	N and V naming	AtDCS improved N and V naming, V > N
Marangolo et al. (2011) [9]	3 nonfluent	Montage B	A/S LIF cortex supraorbital RF	1 mA, 20 min, 5 sessions	Repetition	AtDCS improved articulatory deficits (repetition, reading)
Marangolo et al. (2013) [8]	12 nonfluent	Montage A	A LST cortex supraorbital RF	1 mA, 20 min, 10 sessions	Conversational therapy	AtDCS on Montage B improved language production more than Montage A
		Montage B	A LIF cortex supraorbital RF	1 mA, 20 min, 10 sessions	Conversational therapy	
Marangolo et al. (2013) [7]	8 nonfluent	Montage B	A/S LIF cortex supraorbital RF	1 mA, 20 min, 5 sessions	V naming	AtDCS improved verb naming
Vestito et al. (2014) [11]	2 nonfluent 1 fluent anomic	Montage B	A/S LF supraorbital RF	1.5 mA, 20 min, 10 sessions	N picture naming	AtDCS improved N naming
Marangolo et al. (2014) [6]	8 nonfluent	Montage A	A LST cortex supraorbital RF	1 mA, 20 min, 10 sessions	Conversational therapy	AtDCS on Montage B improved language cohesion more than Montage A
		Montage B	A LIF cortex supraorbital RF	1 mA, 20 min, 10 sessions	Conversational therapy	
Galletta and Vogel (2014) [5]	1 fluent	Montage B	A/S LF supraorbital RF	1 mA, 20 min, 10 days	N and V production V Naming in sentences, conversation	AtDCS improved V production in sentence context
Floel et al. (2011) [15]	9 nonfluent 3 Fluent	Montage C	C/S RT – parietal junction	1 mA, 20 min, 3 sessions	N picture naming	CtDCS not improved picture naming
You et al. (2011) [20]	21 global	Montage A Montage C	A/S LST cortex supraorbital RF C RST cortex supraorbital LF	2 mA, 30 min, 10 sessions	N picture naming, Auditory Verbal Comprehension	CtDCS improved auditory verbal comprehension
Cherney et al. (2013) [12]	1 nonfluent	Montage C	C/S RT cortex supraorbital LF	1 mA, 13 min, 30 sessions	Oral Reading for Language in Aphasia (ORLA)	CtDCS did not improve WAB
Kang et al. (2011) [18]	8 nonfluent 2 fluent	Montage D	C/S RIF cortex supraorbital LF	2 mA, 20 min, 5 sessions	Yes-No questions, N picture naming, word picture matching	CtDCS improved N picture naming
Jung et al. (2011) [17]	10 fluent 26 nonfluent	Montage D	C/S RIF cortex supraorbital LF	1 mA, 30 min, 10 sessions	Many different treatments: MIT, VAT, PACE, cognitive speech therapy	CtDCS improved WAB in fluent aphasia
Rosso et al. (2014) [10]	25 nonfluent	Montage D	C/S RIF cortex supraorbital LF	1 mA, 15 min, 2 sessions	N picture naming	CtDCS was associated with improved N naming only in patients with integrity of the arcuate fasciculus
Marangolo et al. (2013) [32]	8 nonfluent	Montage E	A/C LIF/RIF cortex S LIF/RIF cortex	2 mA, 30 min, 10 sessions	Repetition	Bilateral tDCS improved articulatory deficits
Costa et al. (2014) [30]	1 nonfluent crossed aphasia	Montage E	A/C LIF/RIF cortex S LIF/RIF cortex	1 mA, 20 min, 10 sessions	N and V picture naming	Bilateral tDCS reduced number of cues needed to produce N and V (no difference between N and V score)
Lee et al. (2014) [33]	6 nonfluent and 5 fluent	Montage E	A/C LIF/RIF cortex	2 mA, 30 min, 1 session	N naming	Bilateral tDCS improved naming response times
Marangolo et al. (2014) [31]	8 nonfluent	Montage E	A/C LIF/RIF cortex S LIF/RIF cortex	1 mA, 20 min, 10 sessions	Conversational therapy	Bilateral tDCS improved speech production
Manenti et al. (2015) [34]	1 nonfluent	Montage E	A/C DLPFC	2 mA, 25 min, 20 sessions	Verb production	Bilateral tDCS improved verb production

A = Anodic, C = Cathodic, S = Sham, L = Left, R = Right, ST = Superior temporal, IF = Inferior frontal, N = Noun, V = Verb, WAB = Western aphasia battery.

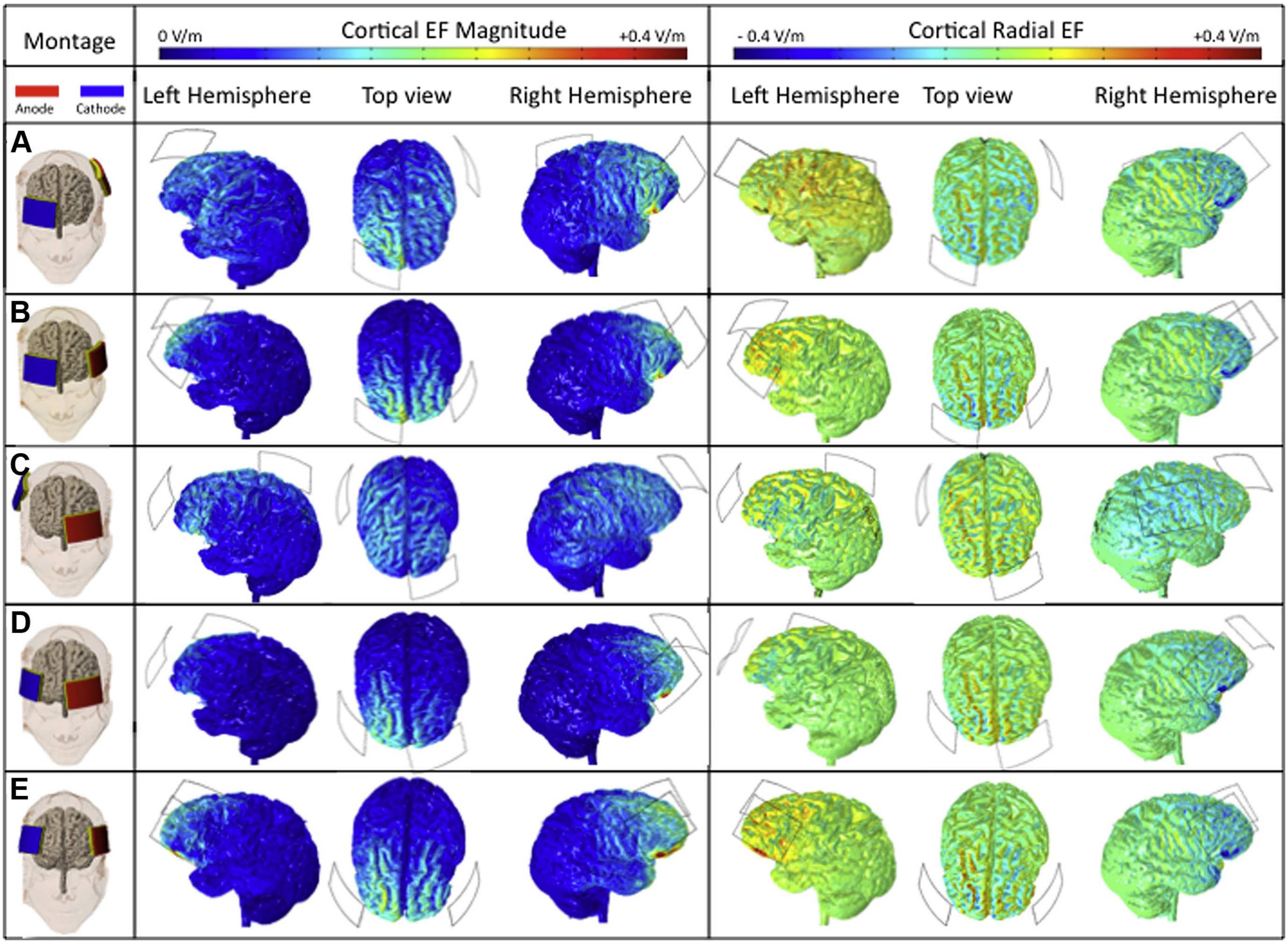

Figure 2. Effect of electrodes' position on cortical electric fields induced by five different montages. An individualized FEM head model was created from MRI scans of an adult male at 1 mm^3 resolution. First column: Sample segmentation head mask showing five electrode montages. Second column: three different views of the EF Magnitude normal to the brain surface showing how each area of the brain is involved in the stimulation. The color maps were generated between 0 and + 0.4 V/m. Third column: three different views of the Radial EF elicited through each gyrus. This measure is sensible to the direction of the current flow. The color maps were generated between −0.4 V/m and +0.4 V/m. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

over the contralateral supraorbital forehead. However, the predicted current flow delivered by the electrode montage in B, produced a higher EF over the perilesional area (see Statistical analyses below). Specifically, montage B generated a clear incoming current (red and yellow colors) over the left perilesional areas and an outgoing current (blue color) over the right frontal region. On the contrary, montage D, with the cathode placed over the right homologue of Broca's area resulted in a higher outgoing current from the underlying right brain region with the anode placed over the left supraorbital cortex.

The model also evidenced that the current distribution in montage E for the bilateral example was only slightly different from Montage B; but the minimal shift of the cathode from the supraorbital right forehead to the right homologue of Broca's area (F6 for the International 10-20 system) produced more outgoing current flow from the right hemisphere (see Fig. 2).

Statistical analysis

Two tridimensional geometric solids, built as parallelepipedes (volume 35 × 18 × 23 mm^3), were inserted into the model. They were accurately placed over the cortex to include the lesion in the left hemisphere and its homologue area in the right hemisphere. We considered the EF value of each grey matter 1 mm^3 voxel inside the left and right box. Totally, we evaluated 21,246 values in the left box and 27,397 values in the right box (see Fig. 3).

The data were not normally distributed (significant Kolmogorov–Smirnov test) because of the intrinsic nature of EF values in brain cortex and they were presented as medians (Interquartile ranges). To compare the magnitude of EF delivered by the five different montages in the same voxel samples, non parametric statistical methods for repeated measures were used: the Friedman's chi-square test for related samples and the non parametric Wilcoxon signed-rank test for paired samples. The size effect P value < 0.05 was considered statistically significant. Bonferoni correction for multiple comparisons was applied dividing the P value by the number of comparisons made. All of the analyses were performed using SPSS v19.

The Friedman test showed significant differences among the montages in both the left and right regions of interest (ROI, chi-square = 19727.5, df = 4, $P < .001$, chi-square = 21624.7, df = 4, $P < .001$).

Moreover, the post-hoc analysis via the Wilcoxon Signed-Ranked test revealed that, in the left perilesional area, the EF magnitude measured for the montage B was higher than the

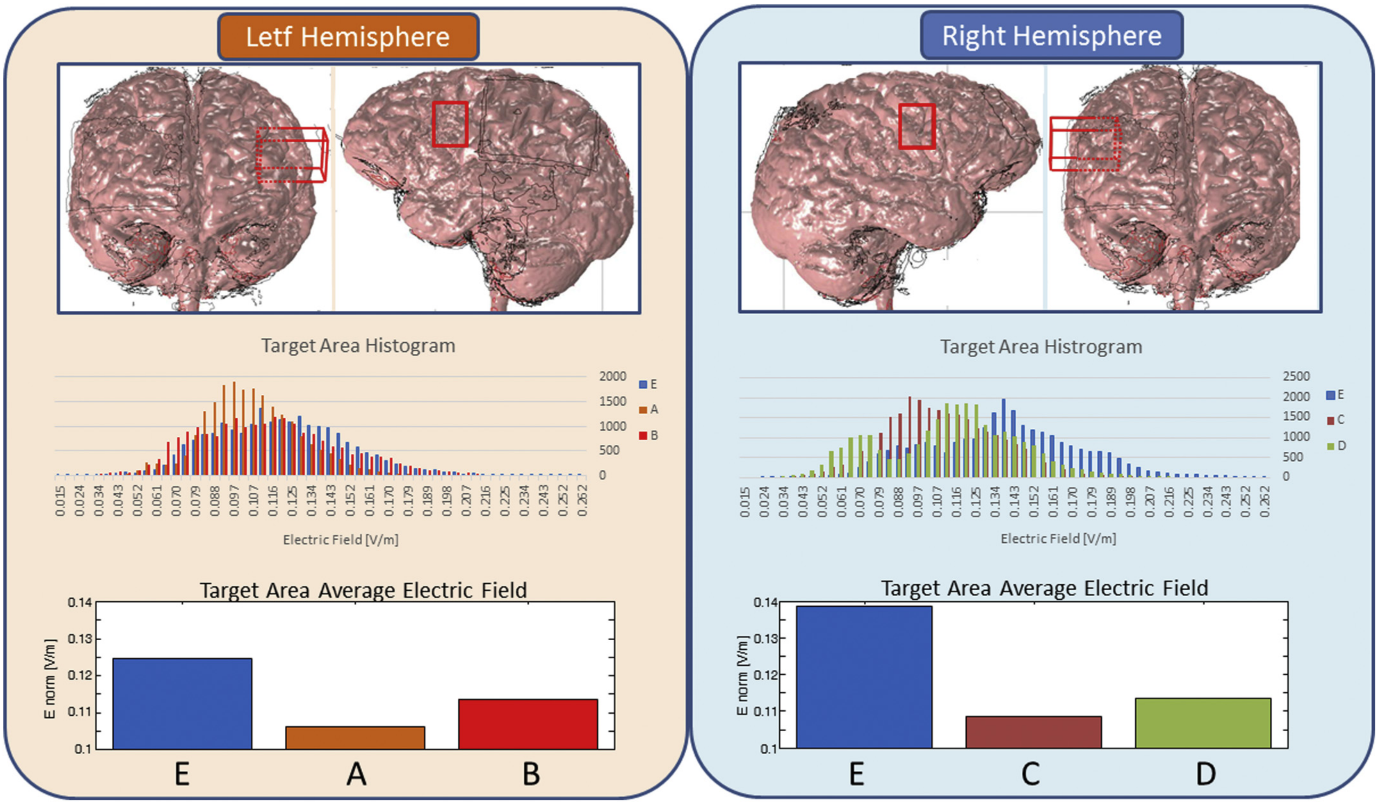

Figure 3. Quantitative analysis. TOP: Selection of target areas: perilesional area (Left Hemisphere) and its homologous (Right Hemisphere) were selected by two 35 × 18 × 23 mm^3 boxes with 1 mm^3 resolution; EF for each voxel inside these boxes belonging to the gray matter were collected for each of the five montages (A, B, C, D, E). MIDDLE: Histogram of EF magnitude on target areas delivered by left (E, A, B) and right hemisphere (E, C, D) targeting montages. *X*-axis indicates the range of EF values divided into a series of small intervals and *Y*-axis indicates the number of times that each EF value falls into each interval. Rightward distributions implies higher EF magnitude values. For both hemispheres, histograms show that the EF delivered by montage E (blue bars) has higher magnitude with respect to the other montages. BOTTOM: Bar plot of EF mean delivered by the left (E, A, B) and the right hemisphere (E, C, D) targeting montages. For both hemispheres, EF mean delivered by montage E (blue bars) has higher magnitude with respect to the other montages. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

montage A, C and D and montage E produced the highest EF magnitude also in the right ROI (see Table 2). This was evidenced by the fact that the sum of ranks of positive differences was higher than the sum of ranks of negative differences in all comparisons ($P < .001$, see Table 3).

Discussion

The aim of the present study was to investigate five electrode montages presently used in tDCS aphasia studies in order to inform researchers regarding the influence of both electrodes on current density and direction when implementing this technique for the promotion of language recovery in post-stroke aphasia. Three main findings deserve discussion: 1) all of the conventional montages A, B, C, and D delivered a diffuse current flow pattern involving both hemispheres. Therefore, even if the so-called “return” electrode is placed over the contralesional supraorbital forehead, this electrode influences the current path through the brain. 2) Current flow patterns during Montages B and D was more efficacious than A and C, because their action was more focused at the targeted area 3) Montage B, although its EF distribution was similar to montage D, exerted a higher EF magnitude effect over the left perilesional cortex, which was even higher in montage E.

As previously summarized, most of the tDCS aphasia studies have used anodic current over the left language areas or cathodic current over the right homologues in order to boost the recovery process in the left undamaged regions [5,21]. The placement of the “return” electrode over the supraorbital region was classically motivated by the assumption that, since this area is not specifically involved in language processing, this electrode would not actively contribute to modulation. Thus, the design and interpretation of most of the research addressed only the current delivered over the

Table 2
Statistical comparisons between the different montages in the left perilesional area (left box) and its right homologue (right box).

		E	A	B	C	D	*P*
Left box							
N 21,246	Median (IQR)	0.1188 (0.045)	0.1043 (0.029)	0.1133 (0.038)	0.1104 (0.047)	0.1004 (0.039)	<0.001
Right box							
N 27,397	Median (IQR)	0.1322 (0.046)	0.1320 (0.053)	0.1186 (0.053)	0.1018 (0.035)	0.1104 (0.042)	<0.001

IQR = interquartile range.

Table 3
Non parametric multiple comparisons (Wilcoxon Signed Rank Test) on the sum of positive and negative ranks differences among the different montages in the left perilesional area (left box) and its right homologue (right box).

Montage	Montage	Sum of positive ranks[a]	Sum of negative ranks[b]	z	P
a) Left box					
E vs.	A	168059093.00	57647788.00	−61.75	<0.001
	B	122469056.50	103237824.50	−10.76	<0.001
	C	131915699.50	93791181.5	−21.32	<0.001
	D	201331152.50	24375728.50	−98.97	<0.001
A vs.	B	70176911.00	155529970.00	−47.74	<0.001
	C	91306941.00	134399940.00	−24.10	<0.001
	D	178577075.00	47129806.00	−73.52	<0.001
B vs.	C	120566429.50	105140451.50	−8.627	<0.001
	D	215326671.00	10380210.00	−114.62	<0.001
C vs.	D	174093376.50	51613504.50	−68.501	<0.001
b) Right box					
E vs.	A	207182375.50	168129127.50	−14.92	<0.001
	B	233101563.00	142209940.00	−34.72	<0.001
	C	310291206.00	65020297.00	−93.68	<0.001
	D	339784062.00	35527441.00	−116.21	<0.001
A vs.	B	247832232.00	127479271.00	−45.97	<0.001
	C	323906132.00	51405371.00	−104.08	<0.001
	D	337963777.50	37347725.50	−114.82	<0.001
B vs.	C	253146966.00	122164537.00	−50.03	<0.001
	D	240907306.50	134404196.50	−40.68	<0.001
C vs.	D	162032446.00	213279057.00	−19.57	<0.001

[a] Sum of positive ranks differences between two montages.
[b] Sum of negative ranks differences between two montages.

targeted region. This led to two neuromodulation strategies: either increasing excitability through anodal stimulation over the left hemisphere [5–9,11,13–16,20,21] or by decreasing excitability in the contralesional language homologue areas using cathodal stimulation in order to attenuate the inhibition from the intact right hemisphere [10,12,15,17–20]. Indeed, while in the context of acute or subacute lesions of the left hemisphere language network there appears to be greater tendency for reallocation of language function into the right hemisphere perisylvian circuits, many studies have shown that, over time, there is, for a number of patients at least, diminished recruitment of right hemisphere structures for language tasks with a redistribution of language processing back to the left hemispheric perisylvian areas [22–24]. However, our computational modeling clearly predicts that the "return" electrode, either selected as an anode or a cathode actively contributes to modulation and current flow between the two electrodes resulting in potential neuromodulation of the region under the reference and between electrodes. Our modeling results support the finding by Moliadze and colleagues [50], which provides some of the strongest clinical evidence to date that the relative position of the stimulation electrode affects neuromodulation under the "active" electrode. Yet, the authors [50] have shown that during weak tDCS, the return electrode is not inert. The modeling results by Datta et al. [40,41,43] support the clinical finding by Moliadze and colleagues that even if the direct actions of the "return" electrode are mitigated by its position or size, the "return" electrode will still influence the current path through the brain from the "active" electrode.

Therefore, in determining electrotherapy dose in tDCS aphasia studies the two stimulating electrodes cannot be considered separately and independently but they influence each other in a mutual way.

The second major finding from our modeling study was that decreasing electrode distance on the head, such as in montage B and D, increased the magnitude of the neuromodulation focused on the targeted region. Indeed, using these montages, a component of incoming current affected the left regions and an outgoing current came from the right hemisphere. Several tDCS studies showed that an incoming current into the cortex generates an excitatory effect depolarizing the neurons invested by the EF and an outgoing current causes a polarization of the neurons promoting inhibition [51,52]. Other studies, more specifically showed how the functional tDCS effects are strongly related to the axonal orientation, able to determine the excitatory or inhibitory nature of the EF delivered [37]. Therefore, although it is challenging to derive physiological effects from structural consideration, it seems likely that, in order to exert the greatest effect over the left hemisphere, it may be better to reduce the inter-electrode distance, such as in montage B and D. Indeed, in montage A and C the current flow pattern was more diffuse over the brain and, therefore, less focalized and thus possibly less effective. Accordingly, many decades ago Rush and Driscoll (1969) [51] already demonstrated that closely spaced electrodes produce a more focal distribution of the EF. The authors also argued that insufficient distance between electrodes reduces current flow and enhances shunting [53]. Therefore, this point in and of itself is not new, yet its application to the tDCS aphasia literature is relevant here since none of the published tDCS aphasia studies in the past few years have focused on this issue and for the most part have neglected the role of the return electrode.

Interestingly, similar EF distribution was delivered with montage B and D. Thus, applying either anodic stimulation over the left Broca's area or cathodic stimulation over the right homologue determines a very similar effect in terms of electrical field. However, since the incoming current into the cortex in montage B was more focally distributed over the perilesional cortex rather than over the entire left cortical areas since there was a lesion, we believe that the most suitable montage using unihemispheric tDCS in aphasia studies might be to deliver anodic stimulation over the left cortical areas placing the cathode over the right contralateral supraorbital forehead.

We also suggest that, given that the cathode placed over the right supraorbital forehead inhibits anyway, it would be worthwhile to place it further back directly over the right homologue of Broca's area and to make it more acutely active in order to maximize its effect. Indeed, in model E the current exerted its greatest excitatory effect over the left perilesional regions when the cathode was over the right Broca's homologue. Following the hypothesis of restoring the excitability unbalance between the right intact and the left damaged hemisphere, the simultaneous excitation of the perilesional left cortex and inhibition of the right homologues increasing the outgoing current could be a crucial point.

We are aware that our results should be interpreted cautiously since a major limitation of this study is that the results were obtained modeling one specific MRI, which, although representative of the most frequently affected lesion area in left-stroke patients, does not resolve the problem of anatomical and functional differences among patients. Furthermore, we also realize that even to make general statements about physical effects is risky based on a single patient, since the impact of interindividual variability is unknown.

However, while these limitations may be overcome by modeling a larger samples of patients, we believe that the conclusion derived from this single patient simulation seems at least to suggest that, if the goal of using tDCS with language treatment is to enhance the language recovery process in the left perilesional areas, it might be better to choose a bilateral electrode montage setting the anode and the cathode electrodes as active electrodes, respectively, over the left language area and their right homologue. Indeed, bilateral tDCS studies in the motor domain have already shown that the simultaneous modulation of the left and right motor area with opposite current is effective for motor recovery [29]. In the language domain, initial studies both in single cases [30,34] and in patient groups [29,30,33] have already confirmed bilateral tDCS efficacy for promoting language recovery which was not limited to treated forms [30] but also generalized to untrained items [32].

While these five initial bilateral tDCS aphasia studies [29,30,32–34] are an exciting first step into extending our understanding of tDCS dose and administration parameters for speech-language deficits post-stroke, more tDCS studies with a larger sample of subjects are needed in order to design optimal electrotherapies as an adjuvant for language recovery in stroke survivors with aphasia.

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