Bilateral Transcranial Direct Current Stimulation Language Treatment Enhances Functional Connectivity in the Left Hemisphere: Preliminary Data from Aphasia

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Abstract

■ Several studies have already shown that transcranial direct current stimulation (tDCS) is a useful tool for enhancing recovery in aphasia. However, no reports to date have investigated functional connectivity changes on cortical activity because of tDCS language treatment. Here, nine aphasic persons with articulatory disorders underwent an intensive language therapy in two different conditions: bilateral anodic stimulation over the left Broca's area and cathodic contralesional stimulation over the right homologue of Broca's area and a sham condition. The language treatment lasted 3 weeks (Monday to Friday, 15 sessions). In all patients, language measures were collected before (T0) and at the end of treatment (T15). Before and after each treatment condition (real vs. sham), each participant underwent a resting-state fMRI study. Results showed that, after real stimulation, patients exhibited the greatest recovery not only in terms of better accuracy in articulating the treated stimuli but also for untreated items on different tasks of the language test. Moreover, although after the sham condition connectivity changes were confined to the right brain hemisphere, real stimulation yielded to stronger functional connectivity increase in the left hemisphere. In conclusion, our data provide converging evidence from behavioral and functional imaging data that bilateral tDCS determines functional connectivity changes within the lesioned hemisphere, enhancing the language recovery process in stroke patients. ■

INTRODUCTION

Over the last few years, several studies have emphasized the use of transcranial direct current stimulation (tDCS), a noninvasive brain stimulation technique, in enhancing healthy performance and stroke recovery (Elsner, Kugler, Pohl, & Mehrholz, 2013). On the basis of early experimental work in animal models, it has been hypothesized that anodal tDCS (A-tDCS) increases cortical excitability, inducing a depolarization of the resting membrane potential and increasing neuronal firing rates. In contrast, cathodal tDCS decreases cortical excitability, shifting the resting membrane potential toward hyperpolarization and reducing the firing rate of neurons (Nitsche & Paulus, 2010). Converging evidence has also suggested that tDCS may provide a supplementary treatment approach for the recovery of language deficits in chronic stroke-induced aphasia. Indeed, persons with aphasia exhibit greater improvement of lexical-retrieval difficulties (Fiori et al., 2011, 2013; Marangolo, Fiori, Di Paola, et al., 2013; Fridriksson, Richardson, Baker, & Rorden, 2011; Baker, Rorden, & Fridriksson, 2010), nonfluent speech (Marangolo et al., 2014; Marangolo, Fiori, Calpagnano, et al., 2013), and articulatory disorders (Marangolo et al., 2011) when the language treatment is coupled with A-tDCS.

In addition to unilateral bipolar stimulation, bilateral bipolar balanced tDCS over the left and right frontal areas has been noted to enhance recovery from articulatory disorders in the aphasia population. This was based on the assumption that upregulating excitability of intact portions of the lesioned hemisphere and downregulating the excitability of the contralesional one would lead to the greatest recovery of language (Marangolo, Fiori, Cipollari, et al., 2013).

Despite this growing body of evidence, so far, how tDCS language treatment may influence brain functional connectivity reorganization in left-stroke patients has never been explored. Recent studies on healthy participants have revealed the potential of resting-state fMRI (rs-fMRI) to map changes of brain activity induced by tDCS (Park et al., 2013; Keeser et al., 2011). However, the majority of these studies have focused on motor cortex stimulation, also including motor activation paradigms (Lindenberg, Nachtigall, Meinzer, Sieg, & Flöel, 2013; Polanía, Paulus, & Nitsche, 2012). Polania et al. (2012), focusing on tDCS-induced changes in the motor

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cortex, revealed that cathodal tDCS over the left motor area (M1) increased local connectedness within M1 during rest, whereas A-tDCS increased long-distance functional connections in M1 (in both conditions, the reference electrode was placed over the right supraorbital region). Lindenberg et al. (2013) assessed the effects of A-tDCS over the left M1 by measuring rs-fMRI before and after an RT task (go–no-go paradigm) performed with the left or the right index finger. The resting-state analysis demonstrated that, compared with sham, A-tDCS decreased connectivity of the right hippocampus and M1 (contralateral to the anode position) while increasing connectivity in the left pFC.

With regard to the language domain, only two studies performed on elderly participants have explored the neural correlates of tDCS. Holland et al. (2011), using task-related fMRI, tested whether A-tDCS over the left inferior frontal gyrus (LIFG) increases picture-naming performance in neurologically unimpaired individuals (n = 10). Results showed that A-tDCS significantly reduced BOLD signal in the left frontal cortex, including Broca's area, compared with sham but had no detectable impact on BOLD response in the surroundings regions. This indicates that A-tDCS exerted a regionally specific rather than global cortical facilitation effect. Meinzer, Lindenberg, Antonenko, Flaisch, and Flöel (2013), using both task-related fMRI and rs-fMRI, explored whether a single session of A-tDCS over the LIFG would improve elderly adults' performance in a semantic word generation task, which is negatively affected by advanced age. In their study, rs-fMRI assessed the impact of A-tDCS on large-scale functional resting state network. Behaviorally, A-tDCS improved performance in older adults up to the level of younger controls. rs-fMRI analysis revealed a decrease in functional connectivity in bilateral frontotemporal cortices (including areas that were hyperconnected during sham-like bilateral IFG), whereas posterior brain regions exhibited increased connectivity. On the basis of studies that linked reduced fMRI activity to superior performance or learning (Meinzer et al., 2012; Brehmer et al., 2011), A-tDCS induced activity decreases were interpreted by the authors as enhanced neural efficiency (Meinzer et al., 2013) measured in terms of more "youth-like" brain response patterns in ROI of the frontotemporal network (Poldrack, 2015).

In summary, it seems likely that, in healthy participants, changes of brain activity induced by tDCS influence distinct areas close to and/or distant from the stimulating electrode (Meinzer et al., 2012, 2013; Holland et al., 2011). However, as far as we know, to date, nothing is known on how tDCS language treatment modulates functional connectivity in the aphasia population. Several fMRI studies assessing recovery from aphasia after brain injury have already suggested that an efficient restoration of language networks depends on reintegration of homolateral predominant areas such as the LIFG (Abel, Weiller, Huber, & Willmes, 2014; Turkeltaub, Messing, Norise, & Hamilton, 2011; Van Oers et al., 2010; Thiel et al., 1998; Ohyama et al., 1996) and the left temporoparietal areas (Baldo, Arévalo, Patterson, & Dronkers, 2013; Fridriksson, Richardson, Fillmore, & Cai, 2012; Van Oers et al., 2010; Weiller et al., 1995), or their neighboring regions (Meinzer et al., 2008; Saur et al., 2006, 2008; Heiss & Thiel, 2006; Crinion & Price, 2005; Breier et al., 2004; Cao, Vikingstad, George, Johnson, & Welch, 1999; Warburton, Price, Swinburn, & Wise, 1999). The assessment of neural changes associated with training-induced modifications of language performance confirmed this prediction. Using fMRI, Vitali et al. (2007) monitored the neural correlates of naming performance in two anomic patients before and after specific language therapy for anomia. In both patients, naming was mainly associated with activations in the nondominant hemisphere before starting speech therapy, whereas perilesional areas of the dominant hemisphere were mainly activated after speech therapy, supporting the role of the perilesional areas for effective recovery (see also Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Meinzer et al., 2008). Indeed, in Fridriksson et al.'s (2012) work, activation increase in left hemisphere perilesional areas was found to be a significant predictor of treatment-related improvement in correct naming; this relationship was strongest in the frontal and left temporal lobe (see also Abel et al., 2014; Baldo et al., 2013). Accordingly, most of tDCS studies on language recovery have applied anodic stimulation over the left language areas with the hypothesis to maximize the recovery process within this hemisphere (see Marangolo & Caltagirone, 2014; Monti et al., 2013, for reviews). More recently, a new tDCS electrode montage was proposed, which uses simultaneous bilateral anodal and cathodal stimulation with the assumption that upregulating excitability of intact portions of the lesioned hemisphere and downregulating the excitability of the contralesional one may potentiate the effect of A-tDCS over the damaged hemisphere (Lefebvre et al., 2012; Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010; Vines, Nair, & Schlaug, 2008). Accordingly, the model of interhemispheric competition between the two hemispheres (akin to models of motor recovery after stroke) predicts that language-related deficits are due to reduced activation from the left lesioned areas and/or excess inhibition exerted over the left hemisphere by the intact right hemispheric areas (Kiran, 2012; Murase, Duque, Mazzocchio, & Cohen, 2004; Belin et al., 1996). Thus, simultaneously stimulating the two hemispheres should lead to the greatest recovery from language. Indeed, Marangolo, Fiori, Cipollari, et al. (2013) applied bilateral anodic ipsilesional stimulation over the left Broca's area and cathodic contralesional stimulation over the right homologue of Broca's area to eight chronic aphasics during an intensive language treatment aimed at the recovery of their articulatory disturbances. Results showed that, after bilateral stimulation, patients exhibited a significant recovery not only in terms of better accuracy and speed in articulating the treated stimuli compared with the sham condition but also in other language tasks (picture description, noun and verb naming,

word repetition, and word reading; Marangolo, Fiori, Cipollari, et al., 2013).

Given all of the above results, in this study, we wanted to assess how spontaneous fluctuations of the BOLD signal detected through rs-fMRI changes because of bilateral tDCS language treatment modulates brain functional connectivity reorganization in a group of aphasic chronic stroke individuals. In particular, as all of our patients have left hemispheric lesions, we wonder if bilateral stimulation coupled with an intensive language training recruits the spared left hemispheric areas leading to better recovery.

METHODS

Participants

Nine left brain-damaged participants (five men and four women) were included in the study. Inclusion criteria were native Italian proficiency, premorbid right-handedness (based on the Edinburgh Handedness Questionnaire; Oldfield, 1971), a single left hemispheric stroke at least 6 months before the investigation (see Figure 1), and no acute or chronic neurological or psychiatric symptoms requiring medication.

The data analyzed in the current study conformed with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and were collected in accordance with the institutional review board of the IRCCS Fondazione Santa Lucia, Rome, Italy. Our named institutional review board specifically approved this study with the understanding and written consent of each participant.

Clinical Data

All patients had nonfluent speech. Eight of nine patients were not able to produce any words in spontaneous production. Their speech was limited to few syllables or words because of their apraxia of speech disorders. Severe articulatory groping and distortions of phonemes were present in naming, repetition, and reading tasks of 20 simple syllables (e.g., PA, MO, FU) and words (e.g., *luna* [moon], *pipa* [pipe]) of a standardized test for the evaluation of articulation (Fanzago, 1983). To thoroughly investigate the aphasics' language performance, each participant was also administered a standardized language test (Esame del Linguaggio II; Ciurli, Basso, & Marangolo, 1996). The test included a picture description task, oral and written noun- and verb-naming (n = 20 for noun naming, i.e., *topo* [mouse]; n = 10 for verb naming, i.e., *correre* [to run], *dormire* [to sleep]), nonword and word repetition, reading and writing under dictation (n = 20, i.e., *letto* [bed], *tavolo* [table]). The test also comprised an auditory picture–word matching task (n = 20) and a simple commands comprehension task (n = 20, i.e., *alzi la mano sinistra* [raise your left hand], *apra il libro* [open the book]). Articulatory errors and distortions of phonemes were present in naming, repetition, and reading. Noun and verb written naming and word writing under dictation were severely impaired. Auditory comprehension abilities were adequate for words and simple commands in the language test (Esame del Linguaggio II; Ciurli et al., 1996), whereas patients still had difficulties in a more complex auditory comprehension task (Token test cut-off 29/36; De Renzi & Faglioni, 1978; see Table 1).

To evaluate nonverbal oral motor skills, the Buccofacial Apraxia Test (De Renzi, Pieczuro, & Vignolo, 1966) was administered. None of the patients showed buccofacial apraxia.

Experimental Design

All participants underwent two tDCS conditions: a real stimulation and a sham condition. In both conditions, 15 daily sessions (Monday to Friday, weekends off, Monday to Friday, weekend off, Monday to Friday) of concurrent speech therapy focused on the treatment of the patients' articulatory disorders were performed (see Figure 2). Although tDCS stimulation was delivered from the beginning of the therapy session for up to 20 min, the language treatment lasted 1 hr/day in both conditions. There was a 14-day intersession interval between the real and the sham condition. The order of conditions was counterbalanced across participants. The study was conducted in a double-blind fashion to guarantee that neither participant nor researcher was aware of the stimulation

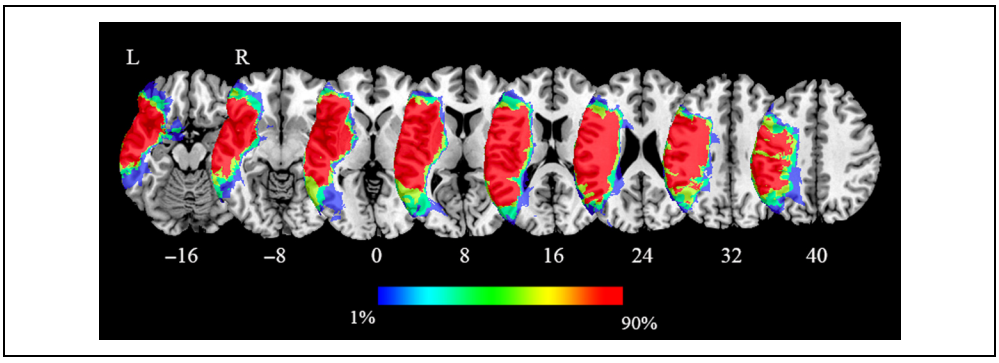

Figure 1. Percentage lesion overlap (1–100%) for all stroke patients. Left Broca's area ([7, −48, 24], MNI coordinates) is included in the most overlapping region, together with the primary sensory–motor cortex (BA 3a), the premotor cortex (BA 6), the primary auditory cortex (TE 1.0), and the insula.

Table 1. Sociodemographic and Clinical Data of the Nine Nonfluent Aphasic Participants

Participant	*Sex*	*Age*	*Ed. Level*	*Time Post-onset*	*PD*	*NN*	*VN*	*WR*	*NWR*	*WRead*	*NWRead*	*Token Test*
1	F	62	8	2 y, 8 mo	0	2.5	5	12.5	17.5	10	7.5	14/36
2	F	55	13	9 mo	0	0	0	0	0	0	0	8/36
3	F	61	13	2 y, 2 mo	0	10	0	10	7.5	30	0	17/36
4	M	59	18	7 mo	0	0	0	0	0	0	0	10/36
5	M	50	18	4 y, 9 mo	0	0	0	10	15	0	0	10/36
6	M	64	8	2 y, 4 mo	0	32.5	10	22.5	25	37.5	30	6/36
7	F	70	18	8 y	0	7.5	0	27.5	12.5	0	0	8/36
8	M	56	13	1 y, 5 mo	0	25	25	55	32.5	37.5	10	15/36
9	M	47	16	7 y	40	55	25	22	50	72.5	27.5	12/36

For each language task, the percentage of correct responses are reported (Esame del Linguaggio II, cut-off 100%, Ciurli et al., 1996; Token test, cut-off 29/36, De Renzi & Faglioni, 1978).

Ed. Level = Educational Level; PD = Picture Descriptions; NN = Noun Naming; VN = Verb Naming; WR = Word Repetition; NWR = Nonword Repetition; WRead = Word Reading; NWRead = Nonword Reading.

condition. At the end of each condition, none of the participants were able to ascertain differences in intensity of sensation between the two conditions, and they were not aware of which condition they were in (O'Connell et al., 2012). The first rs-fMRI scan was conducted before each tDCS procedure (real tDCS or sham), and a second scan was performed at the end of each tDCS procedure (real tDCS or sham).

tDCS

tDCS was applied using a battery-driven Eldith (NeuroConn GmbH, Germany) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 × 7 cm). Real stimulation consisted of 20 min of 2 mA direct current with the anode placed over the ipsilesional and the cathode over the contralesional IFG (F5 and F7 of the extended International 10–20 system for EEG electrode placement). For sham stimulation, the same electrode montage was used. The Eldith DC stimulator has a built-in placebo mode, which was activated by a code number and included ramp periods at the beginning and the end of sham stimulation to mimic the somatosensory artifact of real tDCS. Thus, placebo tDCS could be identified by neither the operator who administered tDCS nor by the subjects participating in the trial (Gandiga, Hummel, & Cohen, 2006).

Language Treatment

Patients were administered all the standardized language tests at the beginning (baseline; T0) and at the end (T15) of each treatment condition. Before the treatment, 160 stimuli (syllables and words) were audibly presented, one at a time, through an audiotape for three consecutive days. The participants had to repeat each stimulus within 20 sec. We identified the stimuli the patients could not correctly produce or always omitted. As all participants failed to correctly produce all the presented stimuli, the entire list was considered. For each participant,

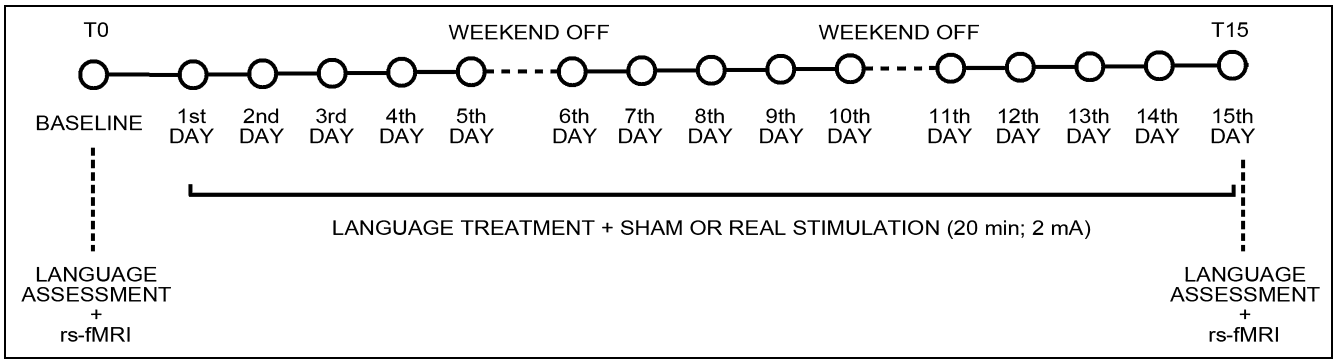

Figure 2. Overview of study design.

the selected stimuli were subdivided into two lists of 80 stimuli. Each list included 28 two-letter syllables (e.g., PA, CA, FU), 12 three-letter syllables (e.g., STA, SPO, TRA), 25 bysyllabic words (CV consonant–vowel, e.g., *luna* [moon] CVCCV, e.g., *palla* [ball]) and 15 trisyllabic words (CV consonant–vowel, e.g., *tavolo* [table]). According to the International Phonetic Alphabet (International Phonetic Association, 1999), syllables included different places (e.g., plosive, nasal, fricative) and manners of articulation (e.g., bilabial, dental, velar). The two lists of words were matched for frequency and length. Each list was randomly assigned to one of the two experimental condition (real vs. sham) and to each participant. In each condition, the order of presentation of stimuli was randomized across the treatment sessions. The therapy method was similar for all patients. For each condition, the whole list of stimuli was presented during each session. The clinician and the patient were seated face-to-face so that the patient could watch the articulatory movements of the clinician as she spoke. The clinician presented one stimulus at a time, and for each stimulus, the treatment involved the use of four different steps, which would progressively induce the patient to correctly reproduce it. Step 1: The clinician audibly presented the entire stimulus and asked the patient to repeat it. If the patient correctly repeated the stimulus, the clinician would present another stimulus, but if he or she made errors the clinician would move on to the next step. Step 2: The clinician audibly presented the stimulus with a pause between syllables, prolonged the vowel sound, exaggerated the articulatory gestures, and asked the patient to do the same. Step 3: As in Step 2, the clinician audibly presented the stimulus, again with a pause between syllables, prolonged the vowel sound, exaggerated the articulatory gestures, and asked the patient to do the same. Step 4: The clinician auditorily presented one syllable at a time, prolonged the vowel sound, exaggerated the articulatory gestures, and asked the patient to do the same.

If the patient was not able to articulate the stimulus in the first step, the clinician would move on to the next step and so on up to the last step. Any time the patient was able to reproduce the articulatory gestures facilitated by the clinician, he or she would be asked to repeat the whole stimulus without the clinician's help and only if he or she succeeded in doing so again the response was considered correct. If the patient was not able to articulate the stimulus in the last step, the response was considered an error. The clinician manually recorded the response type on a separate sheet.

MRI

MRI data were collected using gradient-echo planar imaging at 3T (Philips Achieva, Amsterdam, The Netherlands) using a BOLD T2*-weighted imaging sequence (repetition time = 3 sec, echo time = 30 msec, matrix = 80 × 80, field of view = 224 × 224, slice thickness = 3 mm, flip angle = 90°, 50 slices, 240 vol). A 32-channel receive-only head coil was used (acceleration factor $P = 2$). A T1-weighted whole-brain structural scan was also acquired (1 × 1 × 1 mm voxels). Inside the scanner, participants were instructed to keep their eyes open, to try to think of nothing in particular, and to keep fixating on a central cross on a screen. For the purposes of accounting for physiological variance in the time-series data, cardiac and respiratory cycles were recorded using the scanner's built-in photoplethysmograph and a pneumatic chest belt, respectively.

MRI Preprocessing

Several sources of physiological variance were removed from each individual participant's time-series fMRI data. For each participant, physiological noise correction consisted of removal of time-locked cardiac and respiratory artifacts (two cardiac harmonics and two respiratory harmonics plus four interaction terms), using linear regression (Glover, Li, & Ress, 2000), and of low-frequency respiratory and heart rate effects (Chang & Glover, 2009; Shmueli et al., 2007; Birn, Diamond, Smith, & Bandettini, 2006).

fMRI data were then preprocessed as follows: correction for head motion and slice-timing and removal of nonbrain voxels (performed using FSL: FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Using custom software written in Matlab (The MathWorks, Natick, MA), the six parameters obtained by motion realignment were regressed out, and the data were bandpass-filtered in the frequency range (0.01–0.1 Hz). For group analysis, a two-step registration process was performed. fMRI data were transformed first from functional space to individual participants' structural space using FLIRT (FMRIB's Linear Registration Tool) and then nonlinearly to a standard space (Montreal Neurological Institute MNI152 standard map) using Advanced Normalization Tools (Penn Image Computing & Science Lab, www.picsl.upenn.edu/ANTS/). Finally data were spatially smoothed (5 × 5 × 5 mm FWHM Gaussian kernel).

Ischemic lesions were manually drawn on T1-weighted images, and the VOI (number of voxels) was extracted using ITK-SNAP (Yushkevich et al., 2006) and subsequently normalized to MNI space. Lesion overlay percentage maps were obtained by binarizing (i.e., assigning a value of 0 or 1 to each voxel) the normalized lesion volumes and by calculating the percentage of overlaying voxels.

Network Analysis

A functional connection between two brain voxels was assumed as an undirected and weighted graph link (Caldarelli, 2007), with the weighting being the square of the correlation coefficient of the time series associated to the two voxels (Gili et al., 2013). For each participant, the square value of the $n \times n$ correlation matrix R was calculated (n being the number of voxels of the gray matter considered) and a threshold was applied to ensure that the Erdos–Renyi entropy S of the network (Watts & Strogatz,

1998) was equal two across participants (Hayasaka & Laurienti, 2010). From the resulting matrix, a topological measure was calculated: eigenvector centrality (EC). For rs-fMRI data analysis, eigenvector centrality mapping (ECM; Lohmann et al., 2010) was chosen. ECM is an established graph-based approach that can be used to quantitatively characterize complex network structures across the entire brain without requiring a priori assumptions about the underlying network structures. Given that the impact of tDCS language treatment on resting-state functional connectivity has not been studied so far, ECM is an ideal tool for the present investigation because it allows for assessment of the impact of tDCS not only on one specific network (or a number of arbitrary selected networks) but, rather, it captures complex changes induced by tDCS across the whole brain. The ECM assigns relative scores to all nodes in the network based on the principle that connections to high-scoring nodes (highly connected nodes) contribute more to each score than equal connections to low-scoring nodes (poorly connected nodes; Lohmann et al., 2010). The resulting centrality maps were then transformed (Van Albada & Robinson, 2007) to ensure that they obey a Gaussian normal distribution as required for subsequent statistical tests.

Changes of EC were identified from a permutation-based nonparametric within-subject paired analysis (FSL randomize; Hayasaka & Nichols, 2003; Nichols & Holmes, 2002). This analysis modeled the interaction of the effect of "treatment," namely baseline pretreatment (B) or post-treatment (P), and the effect of "condition," namely sham (S) or tDCS (T). The interaction is described by the contrast (PT–BT) − (PS–BS) and represents tDCS effects controlled by baseline scans. Both positive and negative interaction effects were examined. Conversely, the sham effects were assessed by the contrast (PS–BS) − (PT–BT). Changes were considered as statistically significant at p values of <.001 cluster level uncorrected, corresponding to a minimum cluster size of 100. Permutation-based analyses were done including all brain voxels except those belonging to the ischemic lesions overlay.

Seed-based Analysis

To assess the possible origin of EC changes induced by tDCS, we investigated the patterns of changes of brain voxels' r2 with respect to those regions defined in MNI space from the preceding group EC analysis ((PT–BT) − (PS–BS)). R2 maps for each participant were obtained by calculating the correlation coefficient between the average time series from the ROIs and all voxels of the brain. The square value of the correlation maps was calculated, and the resulting images were combined in a permutation-based nonparametric inference (FSL randomize; Hayasaka & Nichols, 2003; Nichols & Holmes, 2002); both positive and negative interaction effects were examined. Changes were considered as statistically significant at p values of <.001 cluster level uncorrected, corresponding to a minimum cluster size of 100. Permutation-based analyses were done including all brain voxels, except those belonging to the ischemic lesions overlay.

RESULTS

Behavioral Data Analysis

The patients' performance was evaluated by taking into account the mean percentage of response accuracy for syllables and words.

Statistical evaluations were performed using Statistica 10 (StatSoft, Inc., Tulsa, OK). A 2 × 2 repeated-measures ANOVA was run for syllables and words separately. For each analysis, two within-subject factors were included: Time (baseline [T0] vs. end of treatment [T15]) and Condition (Real Stimulation vs. Sham). Interaction was explored using the Bonferroni's post hoc test.

Before and after each treatment session, the patients' responses to the different readministration of the standardized language tests (Esame del Linguaggio II, Ciurli et al., 1996) were also analyzed using chi-square tests.

Impact of Dual tDCS on Behavioral Performance

Syllables

The analysis showed a significant effect of Time (Baseline [T0] vs. End of treatment [T15], $F(1, 8) = 100.70$, $p < .001$). The interaction Time × Condition was also significant ($F(1, 8) = 22.36$; $p = .001$). The Bonferroni's post hoc test revealed no significant differences in the mean percentage of correct syllables between the two conditions at baseline (differences between Real Stimulation vs. Sham = 5%, $p = 1$). However, at the end of the treatment, the mean percentage of response accuracy significantly improved only in the real stimulation condition (real stimulation: differences between T0 vs. T15 = 33%, $p < .001$; sham condition: differences between T0 vs. T15 = 9%, $p = .19$; see Table 2 and Figure 3).

We ran further analysis by adding the Order of condition (real stimulation vs. sham) as fixed factor. The analysis revealed no significant effect of this factor ($F(1, 7) = 1.49$; $p = .26$).

Words

The analysis showed a significant effect of Time (Baseline [T0] vs. End of treatment [T15], $F(1, 8) = 37.38$ $p < .001$) and Condition (Real Stimulation vs. Sham, $F(1, 8) = 6.50$; $p = .03$). The interaction of Time × Condition was also significant ($F(1, 8) = 18.86$; $p = .002$). The Bonferroni's post hoc test revealed no significant differences in the mean percentage of correct words between the two conditions at baseline (differences between Real Stimulation vs. Sham = 1%, $p = 1$). Moreover, the mean percentage of

Table 2. Mean Percentage of Correct Responses for Syllables and Words Before (T0) and After (T15) the Treatment for the Sham and Real Condition, Respectively

Participants	*T0 Sham*	*T15 Sham*	*T0 Real*	*T15 Real*
Syllables				
1	16	37	35	67
2	5	28	26	44
3	7	16	12	33
4	0	2	2	26
5	70	72	47	88
6	19	19	7	35
7	60	65	49	84
8	53	67	31	88
9	56	61	28	72
Mean	**32**	**41**	**26**	**60**
Words				
1	11	27	14	59
2	5	16	14	49
3	14	22	14	35
4	0	0	0	5
5	35	57	38	84
6	24	57	11	49
7	54	68	24	92
8	57	68	58	92
9	26	34	40	69
Mean	**25**	**39**	**24**	**59**

accuracy, although significantly improved in both conditions (real stimulation: differences between T0 vs. T15 = 35%, $p < .001$; sham condition: differences between T0 vs. T15 = 14%, $p = .03$), at the end of the treatment, was significantly greater in the real stimulation than in the sham condition (differences between Real Stimulation vs. Sham at T15 = 21%; $p = .002$; see Table 2 and Figure 4).

We ran further analysis by adding the Order of condition (real stimulation vs. sham) as fixed factor. The analysis revealed no significant effect of this factor ($F(1, 7) = 5.17$; $p = .06$).

Finally, results on the "transfer of treatment effects" in the language examination indicated that, in most of the patients, there was a significant difference in the percentage of correct responses before and after the treatment in different language tasks, which was more pronounced after the real than after the sham condition (see Table 3).

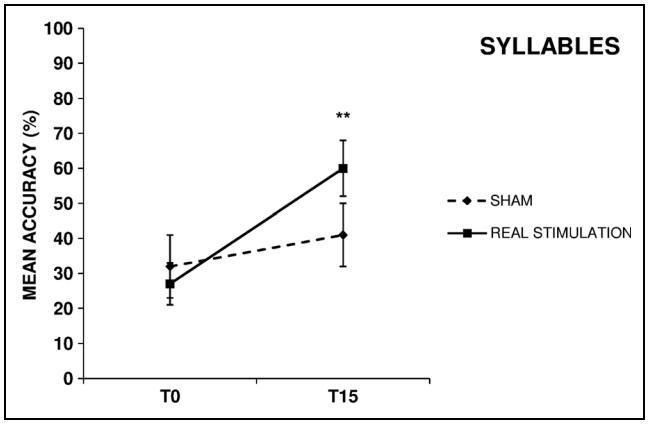

Figure 3. Mean percentage of response accuracy for syllables at baseline (T0) and at the end of treatment (T15) for the real and sham condition, respectively (**$p < .01$). Error bars represent *SEM*.

rs-fMRI Results

EC maps were calculated on networks composed of 60,000 gray matter voxels and thresholded at $S = 2$. The stability of networks across different values of the Erdos–Renyi entropy was explored by Hayasaka and Laurienti (2010). According to the authors, the choice of $S = 2$ ensures the most reliable results after a voxel-based statistical analysis (Hayasaka & Laurienti, 2010). To examine the influence of treatment within-subject analysis, both the tDCS and the sham effect controlling for baseline differences were considered. The (PT–BT) − (PS–BS) contrast (tDCS effect, see Figure 5) revealed that EC increased in the left and right cerebellum ([−3, −78, −28] and [30, −55, −57] MNI space coordinates, respectively), in the left premotor cortex ([−2, −19, 57] MNI space), in the left ACC BA 32 ([−3, 23, 37] MNI space), in the left medial frontal gyrus ([−6, 41, 27] MNI space), in the left precuneus ([−8, −64, 57] MNI space), in the right frontal cortex BA 10 ([8, 60, 28] MNI space), and in the right supplementary

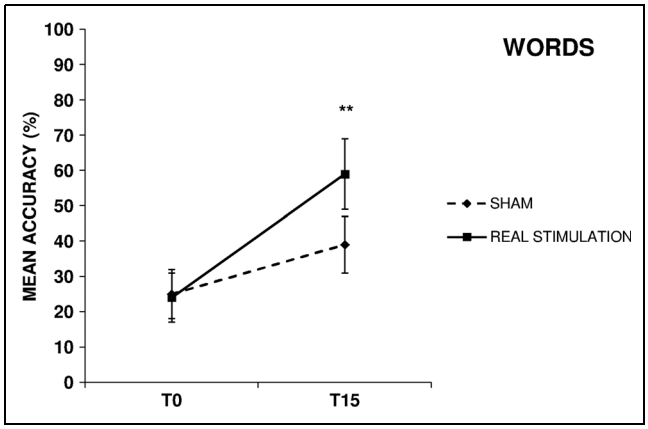

Figure 4. Mean percentage of response accuracy for words at baseline (T0) and at the end of treatment (T15) for the real and sham condition, respectively (**$p < .01$). Error bars represent *SEM*.

Table 3. Mean Percentage of Correct Responses in the Different Language Tasks (Esame del Linguaggio II, Ciurli et al., 1996) at Baseline (T0) and at the End of Treatment (T15) for the Real Stimulation and Sham Condition, Respectively (Cut-off Score 100%)

		Picture Description		*Noun Naming*		*Verb Naming*		*Word Repetition*		*No-word Repetition*		*Word Reading*		*No-word Reading*	
P	*C*	*T0*	*T15*	*T0*	*T15*	*T0*	*T15*	*T0*	*T15*	*T0*	*T15*	*T0*	*T15*	*T0*	*T15*
Sham vs. Real															
1	S	0%	**10%****	2.5%	**22.5%*****	5%	**20%***	12.5%	**37.5%*****	17.5%	**32.5%***	10%	**32.5%*****	7.5%	12.5%
	R	10%	**25%***	22.5%	**50%*****	20%	**50%*****	37.5%	**60%****	32.5%	**55%***	32.5%	**65%*****	12.5%	**32.5%****
2	S	0%	0%	0%	0%	0%	0%	0%	**15%*****	0%	**10%*****	0%	0%	0%	0%
	R	0%	0%	0%	**7.5%****	0%	0%	15%	**45%*****	10%	**25%****	0%	**12.5%*****	0%	5%
3	S	0%	0%	10%	10%	0%	5%	10%	**37.5%*****	7.5%	**22.5%***	30%	27.5%	0%	0%
	R	0%	**50%*****	10%	**52.5%*****	5%	**20%****	37.5%	47.5%	22.5%	**42.5%****	27.5%	**52.5%*****	0%	0%
4	S	0%	0%	0%	0%	0%	0%	0%	0%	0%	5%	0%	0%	0%	0%
	R	0%	0%	0%	0%	0%	0%	0%	2.5%	5%	12.5%	0%	**10%****	0%	**10%****
5	S	0%	0%	0%	**10%****	0%	0%	10%	20%	15%	20%	0%	0%	0%	0%
	R	0%	0%	10%	10%	0%	0%	20%	27.5%	20%	20%	0%	0%	0%	0%
Real vs. Sham															
6	R	0%	**50%*****	32.5%	**57.5%*****	10%	**30%*****	22.5%	**57.5%*****	25%	**52.5%*****	37.5%	**67.5%*****	30%	**60%*****
	S	50%	**20%*****	57.5%	47.5%	30%	20%	57.5%	52.5%	52.5%	47.5%	67.5%	**50%***	60%	50%
7	R	0%	0%	7.5%	**40%*****	0%	**15%*****	27.5%	**75%*****	12.5%	**55%*****	0%	**15%*****	0%	**10%****
	S	0%	0%	40%	30%	15%	15%	75%	70%	55%	60%	15%	12.5%	10%	10%
8	R	0%	**30%*****	25%	**47.5%****	25%	**45%****	55%	**80%*****	32.5%	**72.5%*****	37.5%	**60%****	10%	**22.5%***
	S	30%	20%	47.5%	57.5%	45%	40%	80%	75%	72.5%	75%	60%	62.5%	22.5%	20%
9	R	40%	50%	55%	50%	25%	**40%***	22%	33%	50%	**70%****	72.5%	**85%***	27.5%	27.5%
	S	50%	50%	50%	60%	40%	50%	33%	29%	70%	75%	85%	87.5%	27.5%	40%

The order of conditions was randomized across participants (χ^2 test). Significant results are in **bold**.

P = Participants; C = Conditions; S = Sham; R = Real stimulation.

*$p < .05$.

**$p < .01$.

***$p < .001$.

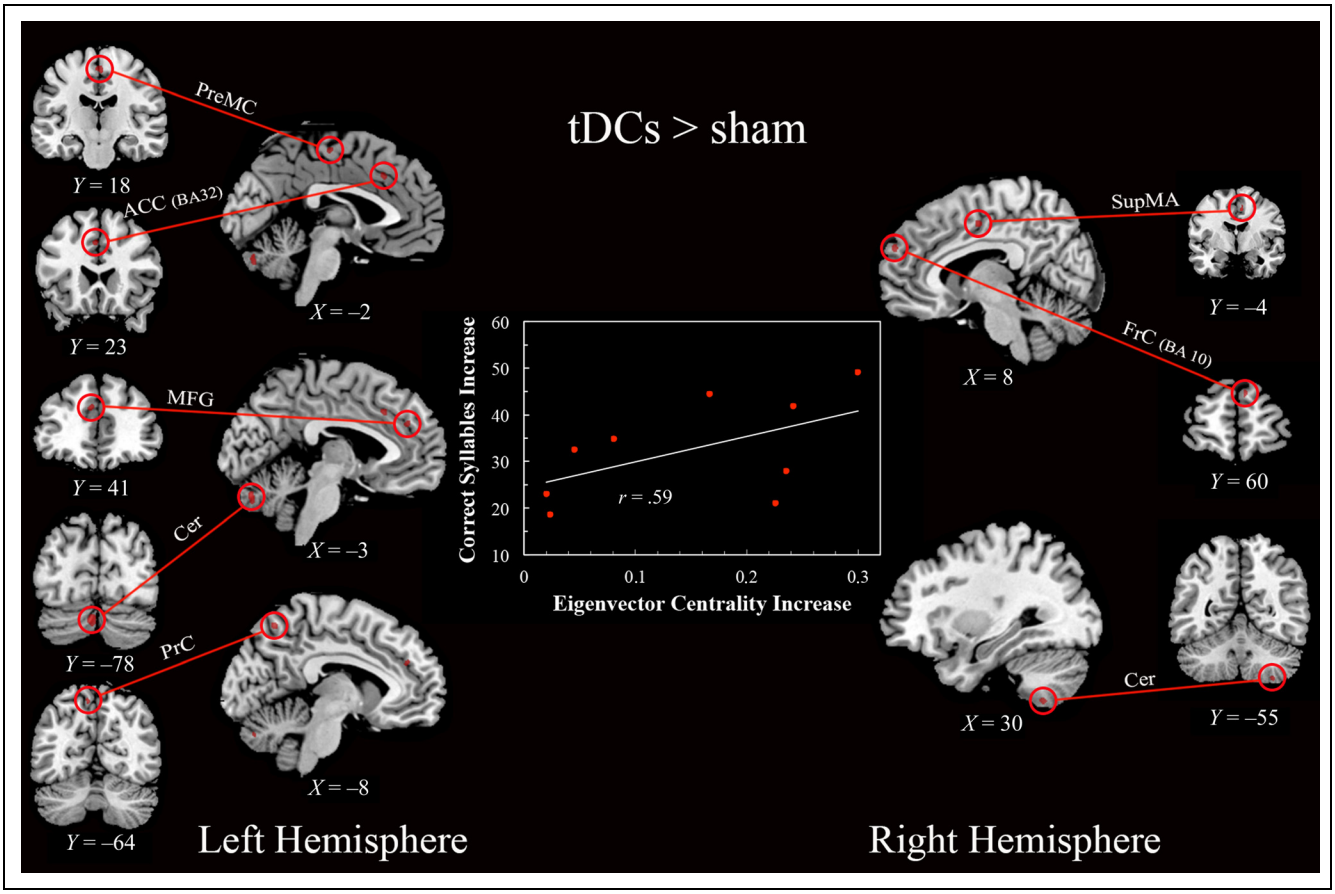

Figure 5. EC changes induced by tDCS + language therapy. The figure shows the baseline-controlled group difference between tDCS and sham administration ((PT–BT) − (PS–BS)), indicating a significant increase of the EC after tDCS language treatment. Signal changes were deemed significant at p values of <.001 cluster level uncorrected, corresponding to a minimum cluster size of 100. The plot shows the correlation between the EC increase and the syllables repetition accuracy increase (r = .59; p < .05). Legend: PT = pLegend: PT = posttreatment tDCS; BT = baseline tDCS; PS = posttreatment sham; BS = baseline Sham; PreMC = premotor cortex; Cer = cerebellum; SupMA = supplementary motor area; ACC = anterior cingulate cortex; MFG = medial frontal gyrus; PrC = precuneus; FrC = frontal cortex; BA = Broadmann's area.

motor area ([8, −5, 46] MNI space; see Table 4 and Figure 5). The consistency between the behavioral results and EC changes induced by tDCS language therapy was investigated. As a result, a significant correlation (r = .59 p < .05) was found between EC increase, calculated within regions coming from the network analysis, and syllables repetition accuracy changes. Conversely, the (PS–BS) − (PT–BT) contrast (sham effect, see Table 5 and Figure 6) returned an increase in the right caudate ([17, 5, 16] MNI space), in the right thalamus ([7, −4, −3] MNI space),

Table 4. Peak Voxel Coordinates: Regions Showing Increases in EC after tDCS

Brain Region	*Cluster Size (Vox)*	*Voxel (x, y, z)*	*Voxel (T)*
Premotor cortex (L)	259	(−2, −19, 57)	4.31
Cerebellum (L)	206	(−3, −78, −28)	4.67
Supplementary motor area (R)	103	(8, −5, 46)	4.60
Anterior cingulate BA 32 (L)	103	(−3, 23, 37)	3.92
Medial frontal gyrus (L)	102	(−6, 41, 27)	3.96
Precuneus (L)	102	(−8, −64,57)	3.69
Frontal cortex BA 10 (R)	101	(8, 60, 28)	3.63
Cerebellum (R)	100	(30, −55, −57)	3.55

Coordinates are reported in MNI space (mm). The voxel size was 1 × 1 × 1 mm, and regions are grouped according to the cluster to which they belong. L = left; R = right; BA = Broadmann's area.

Table 5. Peak Voxel Coordinates: Regions Showing Increases in EC after the Sham Condition

Brain Region	*Cluster Size (Vox)*	*Voxel (x, y, z)*	*Voxel (T)*
Caudate (R)	174	(17, 5, 16)	4.53
Thalamus (R)	144	(7, −4, −3)	4.35
Anterior cingulate BA 32 (R)	105	(5, 13, 32)	4.27
Anterior cingulate BA 24 (R)	100	(7, −15, 44)	4.06

Coordinates are reported in MNI space (mm). The voxel size was 1 × 1 × 1 mm, and regions are grouped according to the cluster to which they belong. L = left; R = right; BA = Broadmann's area.

and in the right ACC BA 32 ([5, 13, 32] and BA 24 ([7, −15, 44] MNI space, respectively; see Table 4). No significant reductions of EC were found in both the tDCS and sham condition.

To investigate the observed centrality changes induced by tDCS, ROI-based functional connectivity analysis was calculated between those regions as they resulted from the group statistics of the EC maps ((PT–BT) − (PS–BS) contrast, i.e., tDCS effect) and the noninjured remaining brain. The analysis showed a network composed by the original seeds and two more regions: the posterior cingulate cortex (bilaterally) and the right Crus I of the cerebellum (Figure 7).

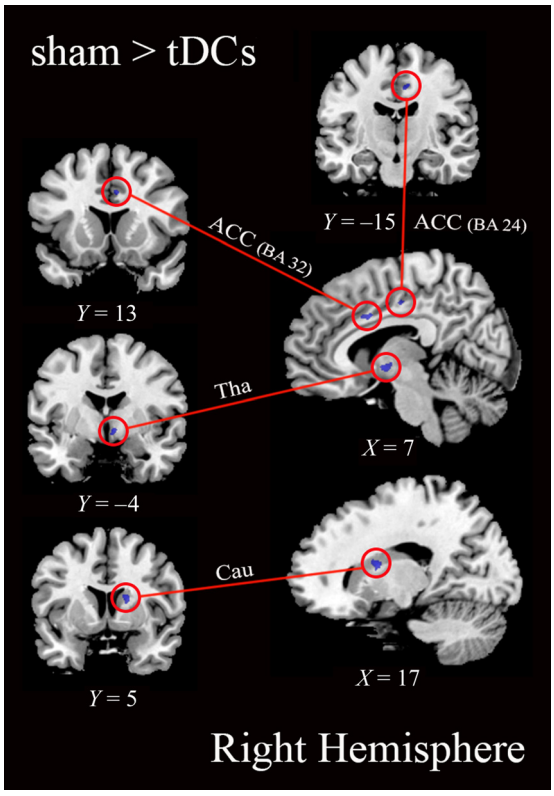

Figure 6. EC changes induced by sham + language therapy. The figure shows the baseline-controlled group difference between sham and tDCS administration ((PS–BS) − (PT–BT)), indicating a significant increase of the EC after the sham language treatment. Signal changes were considered significant at p values of <.001 cluster level uncorrected, corresponding to a minimum cluster size of 100. Legend: PT = posttreatment tDCS; BT = baseline tDCS; PS = posttreatment sham; BS = baseline sham; Cau = caudate; Tha = thalamus; ACC = anterior cingulate cortex; BA = Broadmann's area.

DISCUSSION

This study explored whether bilateral tDCS over the frontal regions would improve language performance and, in particular, the ability to articulate speech in a group of aphasic stroke chronic patients. We also wanted to assess the impact of dual tDCS language treatment on functional connectivity reorganization through rs-fMRI. Behaviorally, the real stimulation condition exerted the greatest influence on the recovery of articulatory errors. Indeed, all patients were faster in repeating the stimuli compared with the sham condition. Coherently with the behavioral data, rs-fMRI results showed an increase of functional connectivity, which, after real stimulation, boosted the recovery process in the left lesioned cerebral hemisphere. In contrast, after the sham condition, connectivity changes were present only in the right brain structures.

Impact of Dual tDCS on Language Performance

Numerous previous studies have already shown that associating specific language training with A-tDCS over the perilesional language areas exerts a positive influence on the recovery of different aspects of speech in the aphasic population (Marangolo et al., 2011, 2014; Fiori et al., 2011, 2013; Marangolo, Fiori, Calpagnano, et al., 2013; Marangolo, Fiori, Di Paola, et al., 2013; Flöel et al., 2011; Baker et al., 2010). However, only one previous study assessed the effects of bilateral tDCS on the recovery of language, showing that the simultaneous stimulation of the frontal regions led to an improvement of articulatory disturbances in a group of eight aphasic individuals (Marangolo, Fiori, Cipollari, et al., 2013). It was speculated that bilateral tDCS had potentiated the effects of anodic stimulation in the left lesioned hemisphere (Marangolo, Fiori, Cipollari, et al., 2013; Fiori et al., 2011; Marangolo et al., 2011) through additional modulation of interhemispheric interactions via cathodic stimulation to the homologue contralesional area (Jung, Lim, Kang, Sohn, & Paik, 2011; You, Kim, Chun, Jung, & Park, 2011; Kang, Kim, Sohn, Cohen, & Paik, 2010). Indeed, unilateral cathodic tDCS, reducing the inhibition over the ipsilesional cortex exerted by the unaffected hemisphere via the transcallosal pathway, determined significant changes in language recovery (Jung et al., 2011; You et al., 2011; Kang et al., 2010). These findings were confirmed and extended in this study. In all participants, behavioral data showed a significant improvement

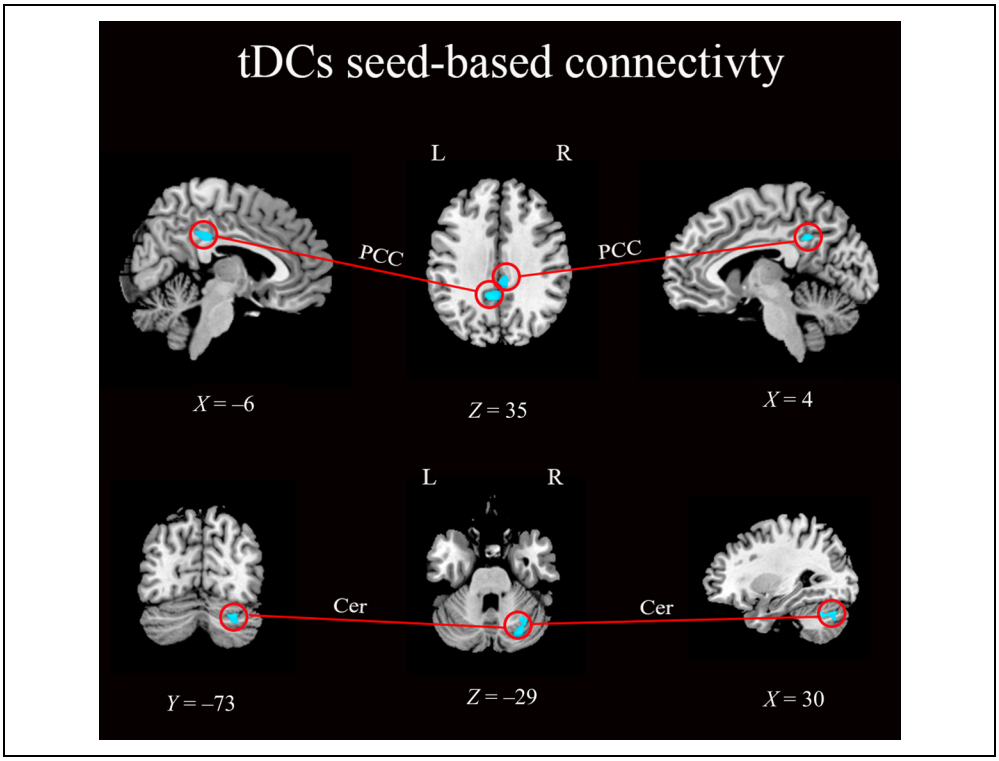

Figure 7. tDCS-driven seed-based R2 connectivity analysis. A paired *t* test was calculated for the condition ((PT–BT) − (PS–BS)). A significant increase of R2 was observed in the posterior cingulate cortex (bilaterally) and in the right Crus I of the cerebellum. Changes were considered as statistically significant at *p* values of <.001 cluster level uncorrected, corresponding to a minimum cluster size of 100. Permutation-based analyses were done including all brain voxels except those belonging to the ischemic lesions overlay.

in response accuracy for syllables in the real condition and words both in the real and sham condition. However, in line with previous work (Marangolo, Fiori, Cipollari, et al., 2013), the real stimulation condition exerted the greatest effects on the production of stimuli not only treated but also belonging to other tasks. Indeed, after real stimulation, most patients were able to correctly produce the whole word and they showed a reduction in phonological errors, the reduction being due to improvement in speech articulation. These results and those of previous behavioral studies using different tasks (see Marangolo & Caltagirone, 2014, for a review; Monti et al., 2013) confirm the potential of tDCS coupled with language training to improve the recovery from aphasia in left-stroke chronic patients.

Impact of Dual tDCS on rs-fMRI

Coherently with the behavioral data, ECM analysis revealed distinct differences in functional connectivity patterns after the real and sham condition. Indeed after real stimulation, increased connectivity was most pronounced in the left brain hemisphere and in both cerebellar hemispheres, which significantly correlates with the amount of improvement found for syllables at the end of the treatment. This correlation was not present for words because, as more complex stimuli, they are more difficult to articulate. Indeed, this has induced a variability in response accuracy across participants, which might have obscured the correlation with the detected functional changes. On the other hand, after the sham condition, functional connectivity changes were accompanied by modulations in different right brain structures.

As previously stated, to our knowledge, the impact of tDCS stimulation with concomitant language treatment on neural functioning has not been studied so far. In the language domain, only few studies, both in the healthy populations, assessed stimulation-induced brain activity during fMRI. In these studies, A-tDCS revealed connectivity changes at the stimulation site (Meinzer et al., 2012; Holland et al., 2011) or in functionally connected distant brain areas (Meinzer et al., 2013). In our study, because all of our patients had severe left-hemispheric stroke, it is reasonable to assume that damage of core language processing areas has favored the recruitment of the right hemisphere (Anglade, Thiel, & Ansaldo, 2014). Indeed, after the sham condition, the language treatment alone determined an enlistment of only right brain structures involving the ACC, the caudate, and thalamus. This suggests that the right hemisphere has actively contributed to the recovery process. In contrast, this pattern was mostly reversed after the real stimulation condition. Indeed, functional connectivity changes were predominantly pronounced in the left hemisphere, suggesting that the simultaneous excitatory stimulation over the left frontal area and inhibition over the contralesional right frontal cortex has disengaged a left functional network leading to the best recovery from language (see also Lefebvre et al., 2012; Lindenberg et al., 2010; Vines et al., 2008, for the motor domain). Therefore, we believe that the recruited regions may be consequences of the effects of treatment and/or stimulation. However, given that most of our patients had lesions involving the LIFG

and the anodic current was delivered over this area, one could argue that the detected positive effect after tDCS was being driven only by the inhibitory stimulation exerted over the right hemisphere. Our recent data from computational modeling on a head of a single left frontal stroke patient suggest that this might not be the case. Indeed, the comparison between different electrode montages showed that bilateral stimulation over the left and right IFG determined a clear incoming current into the left perilesional cortex more focally distributed over the left perilesional region and a component of outgoing current from the right hemisphere compared with unilateral montage with the anode placed over the LIFG (Galletta et al., 2015). Several tDCS studies have shown that incoming current into the cortex generates excitatory effects depolarizing the neurons invested by the electric field whereas outgoing current causes a polarization of the neurons promoting inhibition (Kuo et al., 2013; Nitsche & Paulus, 2000). Therefore, it seems likely that our positive tDCS effects were due to the simultaneous stimulation of the two frontal areas. Thus, we believe that if the goal of using tDCS with language treatment is to boost the language recovery process in the left perilesional areas, it might be better to set the anode and the cathode as active electrodes over the left language area and its right homologue, respectively. In line with this assumption, although the language treatment alone, after the sham condition, resulted in a slight recovery from articulatory disturbances, the real stimulation induced the greatest amount of improvement. Thus, simultaneously stimulating the frontal areas led to the reintegration of homolateral left hemispheric networks. This is in line with several results from task-related fMRI studies, which suggest that, in chronic stroke patients, an efficient restoration of language is more frequently associated with reactivation of left-hemispheric perilesional structures (Abel et al., 2014; Baldo et al., 2013; Saur & Hartwigsen, 2012; Turkeltaub et al., 2011; Van Oers et al., 2010; Crosson et al., 2007). Coherently, the assessment of neural changes associated with training-induced modifications of language performance has already shown that the most effective recovery of language is achieved through a recruitment of left perilesional hemispheric networks (Fridriksson et al., 2012; Vitali et al., 2007; see also Meinzer et al., 2008).

In our study, complex network theory was used to investigate possible changes of brain functional connectivity, induced by tDCS language treatment, without any neuroanatomical a priori assumptions. Specifically, EC was chosen as topological metric to elicit brain nodes, functionally connected to other highly functionally connected nodes (Rubinov & Sporns, 2010). Nodes included in the analysis were selected on the basis of their value of degree centrality, them being part of Erdos Renyi entropy's core definition. Other centrality measures were not considered mainly for computational reasons. Among them, one of the most used is the Betweenness Centrality. It assumes that information travels through a network along the shortest path in a serial fashion. Despite the potential utility of this measure, we believe that it is not ideal for a dynamic system, as is the brain, where information processing follows unrestricted walks, whose lengths may change from one processing to the other. An additional seed-based analysis was used to assess the origin of EC changes in term of network-wise connectivity changes. As a result only a pair of regions showed to be added to the network obtained by EC analysis. Indeed, the pattern of functional connectivity changes, induced by tDCS language treatment, was represented by a network of left hemispheric areas, such as the premotor cortex, the ACC, the precuneus, and the cerebellum, which did not change their connectivity rank, but only the reciprocal level of coordination. Most importantly, because our behavioral treatment was focused on the motor aspects of speech production, we found significant increase in left hemispheric structures related to planning, maintenance, and execution of speech (Rauschecker, Pringle, & Watkins, 2008; Frenck-Mestre, Anton, Roth, Vaid, & Viallet, 2005). Indeed, in the Frenck-Mestre and colleagues' fMRI study on bilinguals (Frenck-Mestre et al., 2005), overt articulation resulted in the bilateral activation of the premotor cortex, the BG, the cerebellum, and the supplementary motor areas, independent of the spoken language. Similarly, in Rauschecker et al.'s (2008) work, the articulation of novel combinations of phonemes forming new words led to the activation of a subset of left hemispheric areas, such as the premotor cortex and the cerebellum. The results of this study confirms the involvement of this network for the motor articulatory component of language, although data from stroke patients also suggest that infarcts of the cerebellum do not always affect only motor control (see Schmahmann, MacMore, & Vangel, 2009).

Taken together, these data confirm the assumption that, although the recruitment of some right hemispheric areas may support recovery (Anglade et al., 2014; Turkeltaub et al., 2011, 2012), increased activity in the right hemisphere does not always lead to the best improvement but may result in a state of abnormal interhemispheric inhibition over the left hemisphere, thus interfering with the recovery process. Indeed, the most consistent effect of repetitive TMS has been sustained improvement in speech production after inhibition of the right frontal area (Barwood et al., 2011; Hamilton et al., 2010; Martin et al., 2009; Naeser et al., 2005). Our findings suggest that bilateral stimulation might have restored interhemispheric unbalance, thus promoting the best outcome for language recovery.

We are aware that the major limitation of our study is represented by the small sample of participants included, which reduces the maximum statistical power available. Nonetheless, even if including a larger sample may favor a better statistical description, we believe that the sample size considered allowed us an adequate statistical control.

It needs also to be acknowledged that, whereas this study reveals the potential of tDCS for the recovery from articulatory disturbances, future studies are required to determine its influence on functional connectivity in the treatment of other language disorders.

Conclusion

In summary, our study provides converging evidence from behavioral analysis and functional imaging that bilateral tDCS combined with specific language training is an effective approach for language recovery after stroke. Most importantly, it shows, for the first time, that tDCS language treatment influences brain functional connectivity reorganization. We believe that future studies, on larger samples of participants, combining tDCS with other brain imaging methods are urgently needed to provide insights into the neural underpinnings responsible for language modifications. Therefore, rs-fMRI could become a valuable tool to explore the effects of tDCS on the aphasic performance and may help to tailor the tDCS procedure to individual needs.

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REFERENCES

Abel, S., Weiller, C., Huber, W., & Willmes, K. (2014). Neural underpinnings for model-oriented therapy of aphasic word production. *Neuropsychologia, 57,* 154–165.

Anglade, C., Thiel, A., & Ansaldo, A. I. (2014). The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: A critical review of literature. *Brain Injury, 28,* 138–145.

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

Baldo, J. V., Arévalo, A., Patterson, J. P., & Dronkers, N. F. (2013). Grey and white matter correlates of picture naming: Evidence from a voxel-based lesion analysis of the Boston Naming Test. *Cortex, 49,* 658–667.

Barwood, C. H. S., Murdoch, B. E., Whelan, B. M., Lloyd, D., Riek, S., O'Sullivan, J. D., et al. (2011). Improved language performance subsequent to low frequency rTMS in patients with chronic non fluent aphasia post stroke. *European Journal of Neurology, 18,* 935–943.

Belin, P., Zilbovicius, M., Remy, P., Francois, C., Guillaume, S., Chain, F., et al. (1996). Recovery from nonfluent aphasia after melodic intonation therapy: A PET study. *Neurology, 47,* 1504–1511.

Birn, R. M., Diamond, J. B., Smith, M. A., & Bandettini, P. A. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *Neuroimage, 31,* 1536–1548.

Brehmer, Y., Rieckmann, A., Bellander, M., Westerberg, H., Fischer, H., & Bäckman, L. (2011). Neural correlates of training-related working-memory gains in old age. *Neuroimage, 58,* 1110–1120.

Breier, J. I., Castillo, E. M., Boake, C., Billingsley, R., Maher, L., Francisco, G., et al. (2004). Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. *Neuroimage, 23,* 1308–1316.

Caldarelli, G. (2007). *Scale free networks*. Oxford: Oxford UP.

Cao, Y., Vikingstad, E. M., George, K. P., Johnson, A. F., & Welch, K. M. A. (1999). Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke, 30,* 2331–2340.

Chang, C., & Glover, G. H. (2009). Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *Neuroimage, 47,* 1448–1459.

Ciurli, P., Basso, A., & Marangolo, P. (1996). *Esame del linguaggio II*. Firenze: Organizzazioni speciali.

Crinion, J., & Price, C. J. (2005). Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. *Brain, 128,* 2858–2871.

Crosson, B., McGregor, K., Gopinath, K. S., Conway, T. W., Benjamin, M., Chang, Y. L., et al. (2007). Functional MRI of language in aphasia: A review of the literature and the methodological challenges. *Neuropsychology Review, 17,* 157–177.

De Renzi, E., & Faglioni, P. (1978). Normative data and screening power of a shortened version of the Token Test. *Cortex, 14,* 41–49.

De Renzi, E., Pieczuro, A., & Vignolo, L. A. (1966). Oral apraxia and aphasia. *Cortex, 2,* 50–73.

Elsner, B., Kugler, J., Pohl, M., & Mehrholz, J. (2013). Transcranial direct current stimulation (tDCS) for improving function and activities of daily living in patients after stroke. *Cochrane Database of Systematic Reviews, 11,* CD009645.

Fanzago, F. (1983). Test di valutazione dell'articolazione. Trattamento Logopedico delle dislalie e delle insufficienze velo-faringee. *Quaderni Acta Phoniatrica Latina, 2,* 80–85.

Fiori, V., Cipollari, S., Di Paola, M., Razzano, C., Caltagirone, C., & Marangolo, P. (2013). tDCS stimulation segregates words in the brain: Evidence from aphasia. *Frontiers in Human Neuroscience, 7,* 269.

Fiori, V., Coccia, M., Marinelli, C. V., Vecchi, V., Bonifazi, S., Ceravolo, M. G., et al. (2011). Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. *Journal of Cognitive Neuroscience, 23,* 2309–2323.

Flöel, A., Meinzer, M., Kirstein, R., Nijhof, S., Deppe, M., Knecht, S., et al. (2011). Short-term anomia training and electrical brain stimulation. *Stroke, 42,* 2065–2067.

Frenck-Mestre, C., Anton, J. L., Roth, M., Vaid, J., & Viallet, F. (2005). Articulation in early and late bilinguals' two languages: Evidence from functional magnetic resonance imaging. *NeuroReport, 16,* 761–765.

Fridriksson, J., Bonilha, L., Baker, J. M., Moser, D., & Rorden, C. (2010). Activity in preserved left hemisphere regions predicts anomia severity in aphasia. *Cerebral Cortex, 20,* 1013–1019.

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

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

Galletta, E., Cancelli, A., Cottone, C., Tecchio, F., Bikson, M., & Marangolo, P. (2015). Use of computational modelling to inform tDCS electrode montages for the promotion of

language recovery in post-stroke aphasia. *Brain Stimulation, 8,* 1108–1115.
Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology, 117,* 845–850.
Gili, T., Saxena, N., Diukova, A., Murphy, K., Hall, J. E., & Wise, R. G. (2013). The thalamus and brainstem act as key hubs in alterations of human brain network connectivity induced by mild propofol sedation. *Journal of Neuroscience, 33,* 4024–4031.
Glover, G. H., Li, T. Q., & Ress, D. (2000). Image based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magnetic Resonance in Medicine, 44,* 162–167.
Hamilton, R. H., Sanders, L., Benson, J., Faseyitan, O., Norise, C., Naeser, M., et al. (2010). Stimulating conversation: Enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. *Brain and Language, 113,* 45–50.
Hayasaka, S., & Laurienti, P. J. (2010). Comparison of characteristics between region- and voxel-based network analyses in resting-state fMRI data. *Neuroimage, 50,* 499–508.
Hayasaka, S., & Nichols, T. E. (2003). Validating cluster size inference: Random field and permutation methods. *Neuroimage, 20,* 2343–2356.
Heiss, W. D., & Thiel, A. (2006). A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain and Language, 98,* 118–123.
Holland, R., Leff, A. P., Josephs, O., Galea, J. M., Desikan, M., Price, C. J., et al. (2011). Speech facilitation by left inferior frontal cortex stimulation. *Current Biology, 21,* 1403–1407.
International Phonetic Association. (1999). *Handbook of the International Phonetic Association: A guide to the use of the International Phonetic Alphabet*. Cambridge University Press.
Jung, I. Y., Lim, J. Y., Kang, E. K., Sohn, H. M., & Paik, N. J. (2011). The factors associated with good responses to speech therapy combined with transcranial direct current stimulation in post-stroke aphasic patients. *Annals of Rehabilitation Medicine, 35,* 460–469.
Kang, E. K., Kim, Y. K., Sohn, H. M., Cohen, L. G., & Paik, N. J. (2010). Improved picture naming in aphasia patients treated with cathodal tDCS to inhibit the right Broca's homologue area. *Restorative Neurology and Neuroscience, 29,* 141–152.
Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., et al. (2011). Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *Journal of Neuroscience, 31,* 15284–15293.
Kiran, S. (2012). What is the nature of poststroke language recovery and reorganization? *ISRN Neurology, 2012,* 786872.
Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., et al. (2013). Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: A neurophysiological study. *Brain Stimulation, 6,* 644–648.
Lefebvre, S., Laloux, P., Peeters, A., Desfontaines, P., Jamart, J., & Vandermeeren, Y. (2012). Dual-tDCS enhances online motor skill learning and long-term retention in chronic stroke patients. *Frontiers in Human Neuroscience, 6,* 343.
Lindenberg, R., Nachtigall, L., Meinzer, M., Sieg, M. M., & Flöel, A. (2013). Differential effects of dual and unihemispheric motor cortex stimulation in older adults. *Journal of Neuroscience, 33,* 9176–9183.
Lindenberg, R., Renga, V., Zhu, L. L., Nair, D., & Schlaug, G. M. D. P. (2010). Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology, 75,* 2176–2184.
Lohmann, G., Margulies, D. S., Horstmann, A., Pleger, B., Lepsien, J., Goldhahn, D., et al. (2010). Eigenvector centrality mapping for analyzing connectivity patterns in fMRI data of the human brain. *PloS One, 5,* e10232.
Marangolo, P., & Caltagirone, C. (2014). Options to enhance recovery from aphasia by means of non-invasive brain stimulation and action observation therapy. *Expert Review of Neurotherapeutics, 14,* 75–91.
Marangolo, P., Fiori, V., Calpagnano, M. A., Campana, S., Razzano, C., Caltagirone, C., et al. (2013). tDCS over the left inferior frontal cortex improves speech production in aphasia. *Frontiers in Human Neuroscience, 7,* 539.
Marangolo, P., Fiori, V., Campana, S., Calpagnano, M. A., Razzano, C., Caltagirone, C., et al. (2014). Something to talk about: Enhancement of linguistic cohesion through tdCS in chronic non fluent aphasia. *Neuropsychologia, 53,* 246–256.
Marangolo, P., Fiori, V., Cipollari, S., Campana, S., Razzano, C., Di Paola, M., et al. (2013). Bihemispheric stimulation over left and right inferior frontal region enhances recovery from apraxia of speech in chronic aphasia. *European Journal of Neuroscience, 38,* 3370–3377.
Marangolo, P., Fiori, V., Di Paola, M., Cipollari, S., Razzano, C., Oliveri, M., et al. (2013). Differential involvement of the left frontal and temporal regions in verb naming: A tDCS treatment study. *Restorative Neurology and Neuroscience, 31,* 63–72.
Marangolo, P., Marinelli, C. V., Bonifazi, S., Fiori, V., Ceravolo, M. G., Provinciali, L., et al. (2011). Electrical stimulation over the left inferior frontal gyrus (IFG) determines long-term effects in the recovery of speech apraxia in three chronic aphasics. *Behavioural Brain Research, 225,* 498–504.
Martin, P. I., Naeser, M. A., Ho, M., Treglia, E., Kaplan, E., Baker, E. H., et al. (2009). Research with transcranial magnetic stimulation in the treatment of aphasia. *Current Neurology and Neuroscience Reports, 9,* 451–458.
Meinzer, M., Antonenko, D., Lindenberg, R., Hetzer, S., Ulm, L., Avirame, K., et al. (2012). Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. *Journal of Neuroscience, 32,* 1859–1866.
Meinzer, M., Flaisch, T., Breitenstein, C., Wienbruch, C., Elbert, T., & Rockstroh, B. (2008). Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *Neuroimage, 39,* 2038–2046.
Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., & Flöel, A. (2013). Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. *Journal of Neuroscience, 33,* 12470–12478.
Monti, A., Ferrucci, R., Fumagalli, M., Mameli, F., Cogiamanian, F., Ardolino, G., et al. (2013). Transcranial direct current stimulation (tDCS) and language. *Journal of Neurology, Neurosurgery & Psychiatry, 84,* 832–842.
Murase, N., Duque, J., Mazzocchio, R., & Cohen, L. G. (2004). Influence of interhemispheric interactions on motor function in chronic stroke. *Annals of Neurology, 55,* 400–409.
Naeser, M. A., Martin, P. I., Nicholas, M., Baker, E. H., Seekins, H., Kobayashi, M., et al. (2005). Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study. *Brain and Language, 93,* 95–105.
Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping, 15,* 1–25.
Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology, 15,* 633–639.

Nitsche, M. A., & Paulus, W. (2010). Transcranial direct current stimulation—Update 2011. *Restorative Neurology and Neuroscience, 29,* 463–492.
O'Connell, N. E., Cossar, J., Marston, L., Wand, B. M., Bunce, D., Moseley, G. L., et al. (2012). Rethinking clinical trials of transcranial direct current stimulation: Participant and assessor blinding is inadequate at intensities of 2mA. *PloS One, 7,* e47514.
Ohyama, M., Senda, M., Kitamura, S., Ishii, K., Mishina, M., & Terashi, A. (1996). Role of the nondominant hemisphere and undamaged area during word repetition in poststroke aphasics. A PET activation study. *Stroke, 27,* 897–903.
Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9,* 97–113.
Park, C. H., Chang, W. H., Park, J. Y., Shin, Y. I., Kim, S. T., & Kim, Y. H. (2013). Transcranial direct current stimulation increases resting state interhemispheric connectivity. *Neuroscience Letters, 539,* 7–10.
Polanía, R., Paulus, W., & Nitsche, M. A. (2012). Reorganizing the intrinsic functional architecture of the human primary motor cortex during rest with non-invasive cortical stimulation. *PloS One, 7,* e30971.
Poldrack, R. A. (2015). Is "efficiency" a useful concept in cognitive neuroscience?. *Developmental Cognitive Neuroscience, 11,* 12–17.
Rauschecker, A. M., Pringle, A., & Watkins, K. E. (2008). Changes in neural activity associated with learning to articulate novel auditory pseudowords by covert repetition. *Human Brain Mapping, 29,* 1231–1242.
Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage, 52,* 1059–1069.
Saur, D., & Hartwigsen, G. (2012). Neurobiology of language recovery after stroke: Lessons from neuroimaging studies. *Archives of Physical Medicine and Rehabilitation, 93,* S15–S25.
Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M. S., et al. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences, 105,* 18035–18040.
Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., et al. (2006). Dynamics of language reorganization after stroke. *Brain, 129,* 1371–1384.
Schmahmann, J. D., MacMore, J., & Vangel, M. (2009). Cerebellar stroke without motor deficit: Clinical evidence for motor and non-motor domains within the human cerebellum. *Neuroscience, 162,* 852–861.
Shmueli, K., van Gelderen, P., de Zwart, J. A., Horovitz, S. G., Fukunaga, M., Jansma, J. M., et al. (2007). Low-frequency fluctuations in the cardiac rate as a source of variance in the resting-state fMRI BOLD signal. *Neuroimage, 38,* 306–320.
Thiel, A., Herholz, K., von Stockhausen, H. M., van Leyen-Pilgram, K., Pietrzyk, U., Kessler, J., et al. (1998). Localization of language-related cortex with 15 O-labeled water PET in patients with gliomas. *Neuroimage, 7,* 284–295.
Turkeltaub, P. E., Coslett, H. B., Thomas, A. L., Faseyitan, O., Benson, J., Norise, C., et al. (2012). The right hemisphere is not unitary in its role in aphasia recovery. *Cortex, 48,* 1179–1186.
Turkeltaub, P. E., Messing, S., Norise, C., & Hamilton, R. H. (2011). Are networks for residual language function and recovery consistent across aphasic patients?. *Neurology, 76,* 1726–1734.
Van Albada, S. J., & Robinson, P. A. (2007). Transformation of arbitrary distributions to the normal distribution with application to EEG test–retest reliability. *Journal of Neuroscience Methods, 161,* 205–211.
Van Oers, C. A., Vink, M., van Zandvoort, M. J., van der Worp, H. B., de Haan, E. H., Kappelle, L. J., et al. (2010). Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. *Neuroimage, 49,* 885–893.
Vines, B. W., Nair, D., & Schlaug, G. (2008). Modulating activity in the motor cortex affects performance for the two hands differently depending upon which hemisphere is stimulated. *European Journal of Neuroscience, 28,* 1667–1673.
Vitali, P., Abutalebi, J., Tettamanti, M., Danna, M., Ansaldo, A. I., Perani, D., et al. (2007). Training-induced brain remapping in chronic aphasia: A pilot study. *Neurorehabilitation and Neural Repair, 21,* 152–160.
Warburton, E., Price, C. J., Swinburn, K., & Wise, R. J. (1999). Mechanisms of recovery from aphasia: Evidence from positron emission tomography studies. *Journal of Neurology Neurosurgery and Psychiatry, 66,* 155–161.
Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of 'small-world' networks. *Nature, 393,* 440–442.
Weiller, C., Isensee, C., Rijntjes, M., Huber, W., Müller, S., Bier, D., et al. (1995). Recovery from Wernicke's aphasia: A positron emission tomographic study. *Annals of Neurology, 37,* 723–732.
You, D. S., Kim, D. Y., Chun, M. H., Jung, S. E., & Park, S. J. (2011). Cathodal transcranial direct current stimulation of the right Wernicke's area improves comprehension in subacute stroke patients. *Brain and Language, 119,* 1–5.
Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., et al. (2006). User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage, 31,* 1116–1128.