Transcranial Direct Current Stimulation Improves Word Retrieval in Healthy and Nonfluent Aphasic Subjects

Valentina Fiori[1], Michela Coccia[2], Chiara V. Marinelli[1,3], Veronica Vecchi[2], Silvia Bonifazi[2], M. Gabriella Ceravolo[2], Leandro Provinciali[2], Francesco Tomaiuolo[4], and Paola Marangolo[2]

Abstract

■ A number of studies have shown that modulating cortical activity by means of transcranial direct current stimulation (tDCS) affects performances of both healthy and brain-damaged subjects. In this study, we investigated the potential of tDCS to enhance associative verbal learning in 10 healthy individuals and to improve word retrieval deficits in three patients with stroke-induced aphasia. In healthy individuals, tDCS (20 min, 1 mA) was applied over Wernicke's area (position CP5 of the International 10–20 EEG System) while they learned 20 new "words" (legal nonwords arbitrarily assigned to 20 different pictures). The healthy subjects participated in a randomized counterbalanced double-blind procedure in which they were subjected to one session of anodic tDCS over left Wernicke's area, one sham session over this location and one session of anodic tDCS stimulating the right occipito-parietal area. Each experimental session was performed during a different week (over three consecutive weeks) with 6 days of intersession interval. Over 2 weeks, three aphasic subjects participated in a randomized double-blind experiment involving intensive language training for their anomic difficulties in two tDCS conditions. Each subject participated in five consecutive daily sessions of anodic tDCS (20 min, 1 mA) and sham stimulation over Wernicke's area while they performed a picture-naming task. By the end of each week, anodic tDCS had significantly improved their accuracy on the picture-naming task. Both normal subjects and aphasic patients also had shorter naming latencies during anodic tDCS than during sham condition. At two follow-ups (1 and 3 weeks after the end of treatment), performed only in two aphasic subjects, response accuracy and reaction times were still significantly better in the anodic than in the sham condition, suggesting a long-term effect on recovery of their anomic disturbances. ■

INTRODUCTION

A number of studies have emphasized the role of noninvasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), in enhancing healthy performance and stroke recovery (Di Lazzaro et al., 2008; Novak et al., 2008; Naeser, Martin, Nicholas, Baker, Seekins, Helm-Estabrooks, et al., 2005; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005). A new technique, transcranial direct current stimulation (tDCS), was recently introduced (Nitsche & Paulus, 2000, 2001). Its effectiveness in promoting the recovery of motor and cognitive functions has already been demonstrated (Kim et al., 2006; Fregni et al., 2005). During tDCS, weak polarizing direct currents are delivered to the cortex via two electrodes placed on the scalp. The nature of the effect depends on the polarity of the current. Generally, the anode increases cortical excitability when applied over the region of interest with the cathode above the contralateral orbit or above the shoulder (as the reference electrode), whereas the cathode decreases it, limiting the resting membrane potential. In particular, during anodic stimulation in healthy subjects, enhanced visuomotor performance (Antal et al., 2004), motor learning (Nitsche et al., 2003), verbal fluency (Iyer et al., 2005), and working memory (Fregni et al., 2005) have been observed. Recent studies of chronic neurological subjects have further demonstrated how increased cortical excitability influences the recovery of motor (Kim et al., 2006), neurological, and psychiatric symptoms (Ferrucci et al., 2008; Mrakic-Sposta et al., 2008; Boggio et al., 2007).

Until now, very few studies have investigated the use of tDCS in the language domain. In a study by Floel, Rosser, Michka, Knecht, and Breitenstein (2008), tDCS was applied over the posterior part of the left perisylvian area (corresponding to Wernicke's area, CP5 according to the

---

[1]University of Rome, Italy, [2]University of Ancona, Italy, [3]IRCCS Fondazione Santa Lucia, Rome, Italy, [4]Auxilium Vitae Volterra, Pisa, Italy

Journal of Cognitive Neuroscience 23:9, pp. 2309–2323

extended International 10–20 System for EEG electrode placement) of 19 healthy individuals while they acquired 30 novel objects' names (nonwords). Each subject underwent one session of anodic tDCS, one session of cathodic tDCS, and one session of sham stimulation. The second electrode (reference electrode) was positioned over the contralateral supraorbital region. During stimulation, subjects were presented with a pair of stimuli (an auditory nonword matched with an object picture) they had to remember. In a subsequent phase, they had to judge whether the picture of the object and the novel word were the same as in the previously presented pair. Outcome measures were learning speed and learning success in acquiring the novel words. Results showed significant effects for both measures only during anodic stimulation of the left Wernicke's area.

Similar results were obtained by Sparing, Dafotakis, Meister, Thirugnanasambandam, and Fink (2008) in a group of 15 healthy subjects who performed a picture-naming task before and after stimulation of Wernicke's area (CP5). In their study, all subjects underwent four sessions of different stimulations: anodic, cathodic, and sham stimulation of the left Wernicke's area and anodic stimulation of the homologous right Wernicke's area. In all conditions, the reference electrode was fixed contralaterally over the orbit. The authors found that the subjects responded significantly faster only following anodic tDCS over the left Wernicke's area.

Except for Monti et al.'s (2008) work, no other study on aphasia has investigated the effect of tDCS on recovery of language functions. These authors reported the effects of tDCS on chronic vascular aphasia. Patients were assigned to an "anodal tDCS" group (4 patients) and a "cathodal tDCS" group (4 patients). The first group underwent anodic and sham tDCS over the left fronto-temporal areas (Broca's region, defined as the crossing point between T3–Fz and F7–Cz according to the extended International 10–20 System for EEG electrode placement), whereas the second group underwent cathodic and sham tDCS over the same region. In both groups, the reference electrode was positioned above the right shoulder. Only cathodic stimulation applied to left fronto-temporal cortex led to a significant improvement of the patients' ability to name pictures of objects. As cathodic tDCS causes a decrement in the excitability of cortical inhibitory circuits, the authors hypothesized that the observed improvement was due to a tDCS-induced depression of cortical inhibitory interneurons, which lead to a disinhibition and, consequently, to improved functioning of the damaged cerebral language areas (Monti et al., 2008).

The abovementioned studies in healthy and brain-damaged subjects suggest that tDCS may be effective in enhancing verbal learning. In the two studies in healthy subjects (Floel et al., 2008; Sparing et al., 2008), the choice to stimulate Wernicke's area was based on results of previous research reporting activation of the temporal regions when subjects performed lexical–phonological retrieval tasks (Watanabe, Yagishita, & Kikyo, 2008; Yagishita et al., 2008; Hickok & Poeppel, 2004; Kikyo, Ohki, & Miyashita, 2002; Kikyo, Ohki, & Sekihara, 2001; Indefrey & Levelt, 2000). Nevertheless, it has not yet been clarified which type of stimulation and which electrode positions have the greatest effect on language improvement. Although both studies in healthy subjects reported a positive effect only for the anodic condition with the stimulation electrode placed over Wernicke's area and the reference electrode above the orbit (Floel et al., 2008; Sparing et al., 2008), Monti and colleagues found that improved performance could be obtained only by applying cathodic stimulation over the damaged left hemisphere regions to inhibit cortical interneuron hyperactivity. Unlike the studies on healthy subjects (Floel et al., 2008; Sparing et al., 2008), Monti et al. (2008) stimulated a fronto-temporal region located anterior to Wernicke's area and used the contralateral shoulder for reference electrode placement. Therefore, the different position of the electrodes, which could have affected the direction of the excitability change, likely explains the different results obtained in the healthy and aphasic groups.

It should be noted that although Monti et al. (2008) demonstrated significant recovery of naming difficulties in the chronic group, they did not report whether the effects persisted after treatment. Recent studies suggest that long-term effects might be more easily obtained with repeated tDCS applications. In a group of depressed subjects, tDCS was applied over left frontolateral dorsal cortex in 10 sessions performed over a 2-week period. The beneficial effects persisted for a month after the end of treatment (Boggio et al., 2007). Similarly, Naeser, Martin, Nicholas, Baker, Seekins, Helm-Estabrooks, et al. (2005) reported improved ability to name pictures 2 and 8 months after rTMS in a case of severe nonfluent/global aphasia when TMS was applied every day over a 2-week period. With regard to motor recovery, it was recently proposed that the greatest improvement is obtained when the damaged areas are stimulated during simultaneous specific motor training for the paretic hand (Bolognini, Pascual-Leone, & Fregni, 2009; Kim et al., 2006). The beneficial effects of anodic tDCS were found for both motor response accuracy and average motor speed (Kim et al., 2006). Bolognini et al. (2009) suggested that noninvasive brain stimulation might enhance the positive effect of motor training by inducing modifications in cerebral plasticity.

It is well known that in aphasic subjects, word-finding difficulties are the most pervasive symptom of language breakdown and that naming disorders lead to a wide variety of errors because of damage to different stages of name processing. Generally, anomic difficulties are due to the inability to retrieve a phonological word form even when the word is recognized (Basso, Marangolo, Piras, & Galluzzi, 2001; Miceli, Amitrano, Capasso, & Caramazza, 1996; Howard, Patterson, Franklin, Orchardlisle, & Morton, 1985). This difficulty is explained in Levelt's model, which suggests that anomic patients are affected by a deficit at the "phonological code" level (Levelt & Meyer, 2000; Levelt, Roelofs, & Meyer, 1999; Levelt, 1992). Levelt showed that although these patients can select the correct lexical item from the "mental lexicon," they can activate the corresponding phonological representation only when they are given very long response times.

In Floel et al.'s (2008) study, the beneficial effects of anodic stimulation during the associative learning task were measured by asking subjects to recognize a previously learned pair of stimuli. In our study, to compare the results of the healthy participants with those of the aphasic patients, tDCS was applied while healthy subjects retrieved verbal stimuli (nonwords) previously associated with a given picture (Experiment 1). In this condition, normal subjects have complete semantic information about the concept (given by the picture) but cannot activate the phonological representation in the mental lexicon because, by definition, the word is not there. We also wanted to determine whether tDCS would improve word-findings recovery in chronic aphasic subjects with an intact semantic component and damage to the phonological output lexicon (Experiment 2).

To determine whether there were any long-term effects of tDCS application (Bolognini et al., 2009) in the aphasic group, stimulation was applied for five consecutive days while the subjects underwent intensive language training to recover their naming difficulties (Basso et al., 2001). Differing from Monti et al.'s (2008) work and in agreement with results obtained in healthy subjects (Floel et al., 2008; Sparing et al., 2008), we used the same stimulation, that is, anodic stimulation over the left Wernicke's area, in both populations. Then, to verify whether the positive effect of anodic tDCS for novel-word learning was specific to the stimulated left language area, in Experiment 1 we used anodic stimulation over right occipito-parietal cortex. Both anodic conditions were then compared to a sham condition in order to exclude the possibility of a general beneficial effect due to language training.

Two groups of subjects were tested. In the first experiment, 10 healthy subjects were asked to learn three lists of 20 novel words each (non words). Each list was associated with a different stimulation condition (anodic and sham over the left Wernicke's area, anodic over the right occipito-parietal area) in a single daily session over three consecutive weeks with a 6-day intersession interval. In the second experiment, three chronic aphasics underwent daily language treatment on two lists of different words, for five consecutive days, each list during a different week period (these word lists, which were unique for each aphasia patient, are explained later, under Experiment 2, Materials section). Two stimulation conditions were performed, namely, anodic and sham stimulation of the left Wernicke's area. Each week a different stimulation condition was adopted. Based on previous results, we expected that normal subjects would respond faster following the anodic than the other stimulations (Sparing et al., 2008; Nitsche et al., 2003). In aphasic subjects, we expected to find a beneficial effect also on response accuracy similar to what has already been found for motor and language recovery (Monti et al., 2008; Kim et al., 2006). To measure the potential, long-term beneficial effects in the aphasic subjects, two follow-up sessions were also carried out 1 and 3 weeks after the end of each treatment condition.

EXPERIMENT 1

The experimental paradigm was previously tested in a study carried out by Basso et al. (2001).

Materials and Methods

Healthy Subjects

Ten healthy right-handed volunteers (7 men and 3 women) participated in the study. All subjects were Italian native speakers aged between 45 and 70 years (mean = 55 years, *SD* = 7.9) with 8 to 17 years of formal education (mean = 14, *SD* = 2.4). The research protocol was approved by the Ethics Committee of Ospedale Riuniti in Ancona, Italy. Subjects gave their informed consent to participate in the study, which was performed in accordance with the ethical standards of the Declaration of Helsinki.

Materials

We developed a set of 60 bisyllabic invented words (nonwords). They were different from Italian words in that they included a consonant cluster and had a one-to-one phoneme-to-grapheme correspondence. We used 20 words for the left anodic condition, 20 for the right anodic condition, and 20 for the sham condition. Sixty pictures of low, medium, and high familiarity belonging to different semantic categories (animals, tools, body parts, clothes, fruits and vegetables, musical instruments) were selected from Snodgrass and Vanderwart's (1980) picture set. The 60 pictures were randomly matched to the invented words, one picture per word, with the same number of low, medium, and high familiarity pictures in the three conditions.

Procedure

Subjects were tested individually in a single daily session that lasted approximately 35 min. The experiment included three phases: training, verification, and word retrieval. tDCS was applied only during the third phase. Three experimental conditions were used in a randomized counterbalanced double-blind design over a 3-week period: anodic stimulation of the left Wernicke's area and, as a control, sham stimulation in the left Wernicke's area and anodic stimulation of the right occipito-parietal area. During each condition, the subject was required to learn a list of 20 invented words (see Figure 1).

In the first two sessions, stimuli were presented on a PC screen using the E-Prime program (version 2.0). In the last

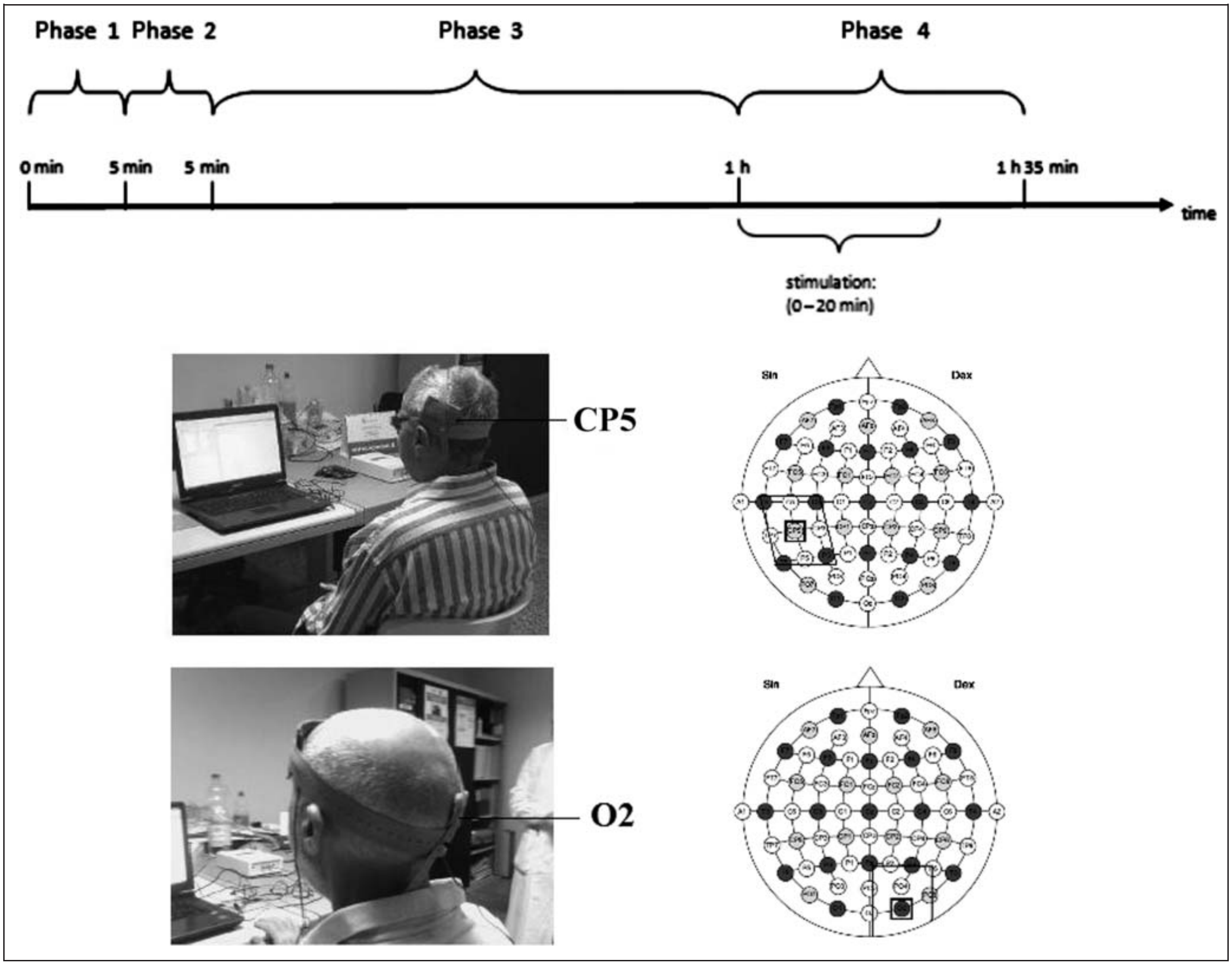

Figure 1. Overview of study design for healthy controls. Each subject underwent three separate stimulation sessions: anodic tDCS over CP5, anodic tDCS over O2, and sham stimulation. The order of the sessions was counterbalanced across subjects. At the start of each session, subjects performed an associative learning task (for about 5 min) in which they were presented with 20 new written "words" (legal nonwords arbitrarily assigned to 20 different pictures) (Phase 1). In the second phase, they had to judge whether or not the pairing corresponded to the previously presented nonword picture matching (Phase 2). In Phase 3, after the stimulation sites were identified, tDCS started simultaneously with the picture-naming task where the subject was expected to name each picture aloud, and which lasted for a total of 20 min; the naming task was interrupted after 35 min. This last phase was used for the healthy controls as well as for the aphasic patients.

session, stimuli were presented with MatLab (Mathworks, Natick, MA), which allowed us to record the subject's vocal responses using an external microphone connected to a portable PC.

Training (Phase 1). The training phase procedure was identical in the three stimulation conditions. Twenty pictures were presented to the subject one by one in the center of the computer screen in pseudorandom order together with the written corresponding invented word (nonword). A fixation point appeared at the center of the screen for 800 msec prior to stimulus presentation, which lasted 4 sec. The interstimulus interval was also 4 sec. The 20 pictures were presented twice in pseudorandom order. The subject was instructed to pay attention to each word–picture pair without reading the word aloud and to memorize the pair of stimuli.

Verification (Phase 2). The 20 stimulus pairings (picture/nonword) were presented to the subject one at a time in the center of the computer screen. In 60% of the pairings, the stimuli corresponded to the previously presented pairings (for example, the picture of the "tent" was correctly matched with the nonword "dresi"), whereas in the remaining 40% the pairings were incorrect (for example, the picture of the "tent" was associated with the nonword "fimpo"). As in the previous phase, a fixation point lasting 800 msec preceded presentation of each pair of stimuli, which remained on the screen for 4 sec. There was a 4-sec interstimulus interval between pairings. The subject had to press the computer bar when the pairing was correct. If the task was performed correctly, a positive feedback appeared on the computer screen (i.e., the word "RIGHT!"); if it was performed incorrectly, a negative feedback appeared (i.e., the word "ERROR!").

Transcranial direct current stimulation (Phase 3). In the last phase prior to the learning phase, tDCS was applied using a battery-driven Eldith (neuroConn GmbH, Ilmenau, Germany) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 cm × 7 cm). A constant current of 1 mA intensity was applied on the skin for 20 min. If applied according to safety guidelines, tDCS is considered to be a safe brain stimulation technique with minor adverse effects (Poreisz, Boros, Antal, & Paulus, 2007; Nitsche et al., 2003). Two different electrode montages were used: The first electrode (which refers to polarity) was placed over CP5 of the extended International 10–20 System for EEG electrode placement. This site has been found to correspond best to the left Wernicke's area, including the posterior part of the superior temporal gyrus, the posterior portion of the middle temporal gyrus, the inferior part of the supramarginal and angular gyri, and part of the middle and inferior occipital gyri (Olivieri et al., 1999; Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994), and has been used in a number of previous tDCS studies (Floel et al., 2008; Sparing et al., 2008) (see Figure 2). The occipito-parietal area of the right hemisphere was stimulated over O2. The reference electrode was placed over contralateral fronto-polar cortex (Sparing et al., 2008; Nitsche & Paulus, 2000).

Overall, three different stimulation sessions were carried out: (1) anodic (CP5-A) stimulation of the left Wernicke's area, (2) anodic (O2-A) stimulation of right occipito-parietal cortex, and (3) sham stimulation (CP5-S). Sham stimulation was performed exactly like anodic stimulation of the left Wernicke's area, but the stimulator was turned off after 30 sec. Although application of tDCS should have minimal or no somatosensory effects that could confound either behavioral or sham conditions, some subjects feel the electrical current as an itching sensation beneath both electrodes during the early rising phase of the direct current, that is, during the first few seconds of stimulation. Our sham protocol ensured that subjects would feel the initial itching sensation at the beginning of tDCS and prevented any real modulation of cortical excitability by tDCS. It has been shown that this procedure makes it possible to blind subjects as to the respective stimulation condition (Gandiga, Hummel, & Cohen, 2006). Furthermore, to ensure the double-blind procedure, the examiner was not told which stimulation was being applied and the stimulator was turned on by another person. Each condition was delivered once a day, 5 days a week, for 3 weeks, with a

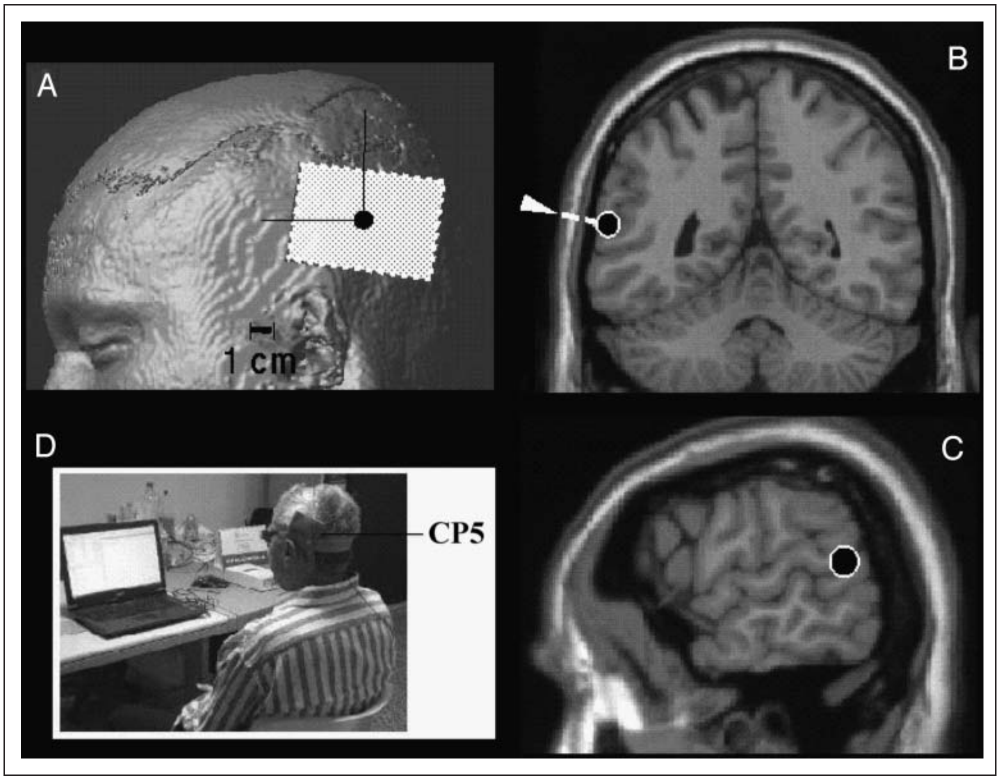

Figure 2. Localization of the tDCS area. The tDCS area was mapped onto the MNI standard space (Collins, Neelin, Peters, & Evans, 1994) using DISPLAY, an interactive program developed at the Montreal Neurological Institute by J.D. MacDonald (www.bic.mni.mcgill.ca/software/Display/). (A) Scalp 3-D reconstruction in the MNI standard space. The white rectangle indicates the position of the tDCS area and the black circle represents the CP5 electrode. Starting from the tDCS and CP5 areas reconstructed on the scalp, perpendicular lines were drawn from the vertex of each rectangle and from the center of the black circle up to the underlying cerebral cortex site (a similar procedure was used in Olivieri et al., 1999). Then, the points found on the cortex were defined as MNI standard space coordinates and drawn on Brodmann's map. The coordinates of CP5 were $y = -51$, $z = -14$; and for the rectangle vertices, y and z coordinates were: (I) −27, 40; (II) −79, 34; (III) −66, −8; and *IV) −20, −7. Based on the reconstructed delimitation of the tCDS and CP5 areas, CP5 was positioned in the posterior part of the superior temporal gyrus (Wernicke's area) and the tDCS area together with the posterior part of the superior temporal gyrus, included the posterior portion of the middle temporal gyrus, the inferior part of the supramarginal and angular gyri, and part of the middle and inferior occipital gyri. (B and C) The black circle on the brain indicates the approximate position of CP5 electrode. (D) One subject's CP5 and tCDS areas.

6-day intersession interval. The order of conditions was varied across subjects to control for learning effects, to avoid carryover effects, and to guarantee sufficient washout of the effects of the previous condition, respectively.

Word retrieval (Phase 4). Once the electrodes had been placed on the scalp, the subjects performed the naming task while they received 20 min of tDCS. Actually, according to a report in the literature (Floel et al., 2008), the overall task was designed to last 35 min (see Figure 1). A different list of 20 stimuli was used for each condition. In this phase, the subjects were instructed to name aloud the picture presented on the PC monitor (screen size 15 inch, viewing distance 1 m) using the corresponding previously matched invented written word. Each picture was preceded by a fixation point, which lasted 800 msec. The stimulus was presented for 4 sec and was followed by a 4-sec interstimulus interval. Vocal response times were recorded through a USB microphone starting when the picture appeared and ending when the first phoneme of the word was produced (McCally USB microphone, Irwindale, CA). If the subject named the picture correctly, the PC recorded the vocal response time and the examiner manually recorded the response type on a separate sheet. If the subject did not respond within 4 sec or responded incorrectly, the picture was presented again together with the corresponding invented written word and the subject was requested to read the word aloud. The same procedure was applied for each of the 20 pictures and was repeated for 35 min or for a maximum of 20 trials. The order of item presentation was randomized across trials. To measure baseline performance, before beginning the word retrieval phase in each condition, the subjects were presented with the corresponding list of pictures and were asked to name aloud each picture, where no written nonword was shown.

EXPERIMENT 2

Aphasic Subjects

Three subjects (3 men) who had had suffered a single left hemispheric stroke were included in the study. Inclusion criteria for the study were native Italian proficiency, premorbid right handedness, a single left hemispheric stroke at least 6 months prior to the investigation, and no acute or chronic neurological symptoms requiring medication. The data analyzed in the current study were collected in accordance with the Declaration of Helsinki and the Institutional Review Board of the Ospedale Riuniti Torrette in Ancona, Italy. Prior to participation, all patients signed informed consent forms. Aphasic disorders were assessed using standardized language tests (i.e., Battery for the Analysis of Aphasic Disorders [BADA], Miceli, Laudanna, Burani, & Capasso, 1994; Token Test, De Renzi & Vignolo, 1962). Subjects were also administered a Neuropsychological Battery (Zimmermann & Fimm, 1994; Orsini et al., 1987) to exclude the presence of attention and memory deficits that might confound the data.

Clinical Data

In all patients, MRI revealed an ischemic lesion involving the left hemisphere (see Figure 3). As shown in Figure 3, the tDCS area did not overlap with M. B.'s lesion; it overlapped U. P.'s lesion only in the damaged most inferior rostral part of the supramarginal gyrus; in M. T., the tDCS area completely overlapped in the damaged posterior regions in the posterior portion of the superior temporal gyrus, the inferior rostral part of the angular gyrus, and the inferior portion of the supramarginal gyrus. The three subjects were classified as nonfluent aphasics because of their poor spontaneous speech with frequent anomia. However, none of the patients had articulatory disturbances which would have confounded data collection. Their comprehension abilities were functionally adequate on the Token Test on which they obtained scores of moderate (M. B., U. P.) to medium severity (M. T.) (see Table 1) (the cutoff score which discriminates between pathological and normal performance is 29/36).

Materials

Before the training, 186 pictures of different semantic categories (animals, furniture, tools, fruits, clothes) were selected and frequency varied from low to high. The pictures were presented once on a PC screen for three consecutive days and the participants had to respond within 15 sec. We identified the pictures the patients could not name and always omitted (M. T. 80/186; M. B., 82/186; U. P. 76/186) and presented them aloud, with a spoken name by the therapist, three times for comprehension, once with the correct name, once with a semantic alternative, and once with an unrelated name (i.e., table → table, writing desk, and car, respectively); the patient had to judge whether or not the name was correct by saying YES or NO. The subjects made no errors on this task.

The experimental naming treatment included only the pictures the patients always responded correctly to, during the comprehension task.

Procedure

Treatment

For each subject, the selected pictures were subdivided into two groups of 40 pictures for M. T., 41 for M. B., and 38 for U. P., controlled for frequency and length. One group of pictures was used for the anodic and one for the sham left Wernicke's stimulation.

As results on healthy subjects have demonstrated the absence of a significant right anodic stimulation effect, we omitted this condition to avoid tiring the aphasic subjects. In each stimulation condition, the treatment was carried out for five consecutive days in one week. The two conditions

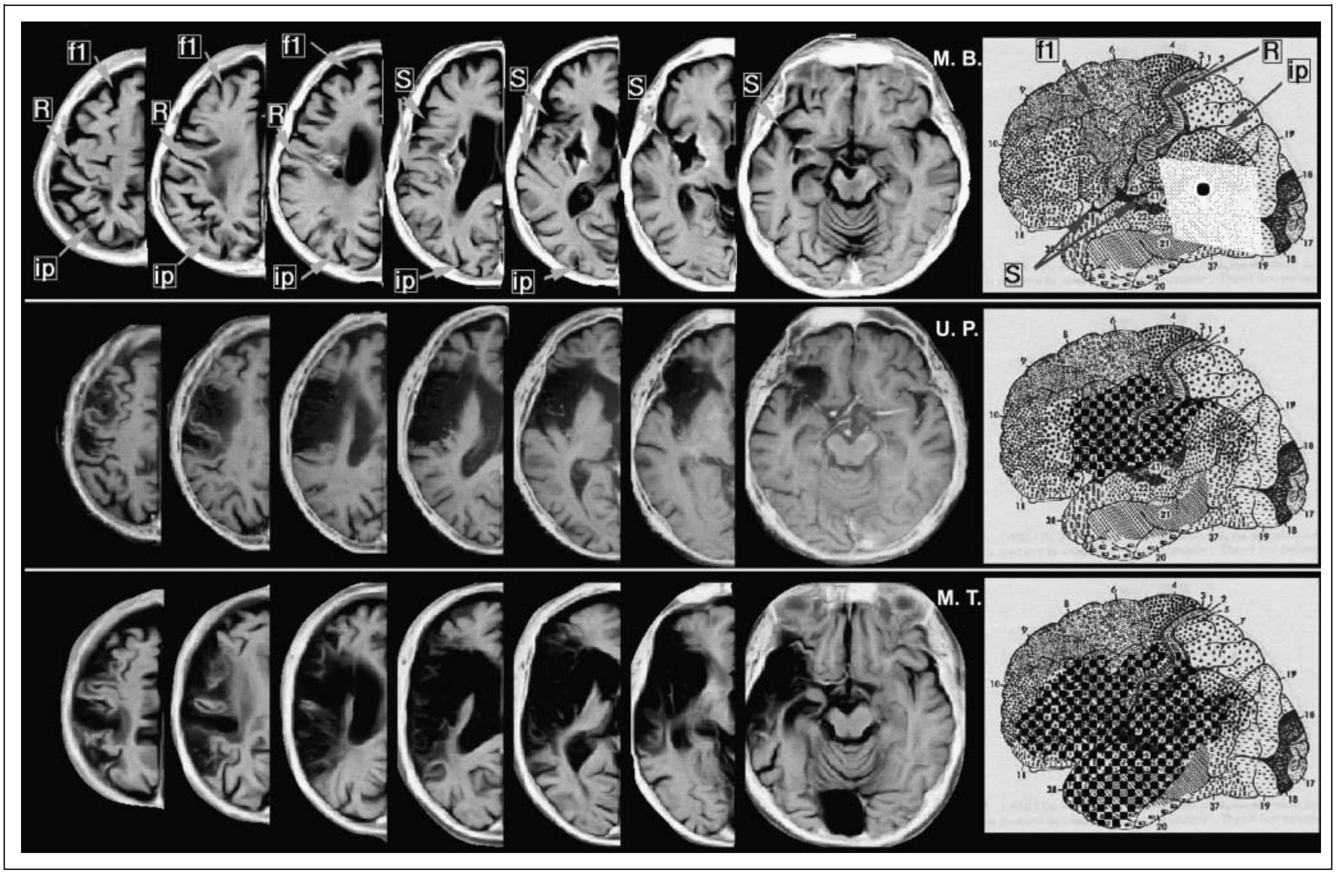

Figure 3. Lesion descriptions for each aphasia patient. M. B.'s lesion is localized in the left insula; it spares most of the cortex (Broca's area) but includes the extreme capsule, the external capsule, part of the internal capsule, the claustrum, the putamen, and part of the ventrolateral thalamus. Small, punctate lesions are present deep to the precentral and postcentral gyri in the periventricular white matter area, adjacent to the body of the lateral ventricle (deep to the motor/sensory cortex area for mouth). U. P.'s lesion extends into fronto-opercular cortex (involving Broca's area) and the postcentral gyrus. The underlying white matter is damaged. The lesion also includes insular cortex, the claustrum, the extreme and the external capsule up to the putamen. Lesion is also present in white matter deep to Broca's area, involving the medial subcallosal fasciculus area (anterolateral to the frontal horn and near the head of the caudate) and less than half periventricular white matter area adjacent to the body of the lateral ventricle, deep to the motor/sensory cortex area for mouth (see Naeser, Palumbo, Helm-Estabrooks, Stiassny-Eder, & Albert, 1989). M. T.'s lesion involves the fronto-temporo-parietal cortical and subcortical regions supplied by the middle cerebral artery, including the inferior frontal gyrus (Broca's area) and a large part of the middle frontal gyrus, part of the most lateral orbito-polar frontal and insular cortex, the temporal pole, the full extension of the superior temporal gyrus, the anterior half of the middle temporal gyrus, the inferior part of the postcentral gyrus and of the anterior supramarginal gyrus. The posterior part of the supramarginal gyrus and the posterior part of the angular gyrus are spared. Subcortical structures are also damaged including the extreme capsule, claustrum, external capsule, putamen, and internal capsule up to the thalamus. The latter appears atrophic. Under the left occipital lobe, into the posterior fossa, an asymptomatic cyst is present. Extensive lesion is also present in the medial subcallosal fasciculus area (anterolateral to the frontal horn) and in about half of the periventricular white matter area adjacent to the body of the lateral ventricle. As shown in the right panels of the figure, the tDCS area does not overlap M. B.'s lesion; in U. P., the tDCS area overlaps only with the damaged most inferior rostral part of the supramarginal gyrus; in M. T., the tDCS area completely overlaps with the damaged posterior regions, specifically in the posterior portion of the superior temporal gyrus, the inferior rostral part of the angular gyrus, and the inferior portion of the supramarginal gyrus. Arrows indicate: (R) Rolandic (central) sulcus, (S) Sylvian (lateral) fissure, (f1) superior frontal sulcus, (ip) intraparietal sulcus.

Table 1. Sociodemographic and Clinical Data of the Aphasic Subjects

Participants	*Sex*	*Age*	*Educational Level*	*Time Post Onset*	*Type of Aphasia*	*Noun Naming (BADA)*	*Noun Compreh (BADA)*	*Token Test*	*Phrase Length*
M. B.	M	65	13	1 year and 9 months	Mild Nonfluent	23/30	40/40	24/36	3–4 words
U. P.	M	74	13	5 years and 11 months	Moderate Nonfluent	25/30	40/40	27/36	2–3 words
M. T.	M	45	18	3 years and 4 months	Severe Nonfluent	4/30	40/40	13/36	1–2 words

noun compreh = noun comprehension.

were presented across subjects in pseudorandom order; the time interval was one week. The training was performed using the same method as in the healthy subjects' third experimental phase. In particular, after applying the electrodes and turning on the tDCS, we instructed subjects to name the pictures that appeared on the PC screen for 15 sec. As in the previous experiment, a microphone recorded vocal reaction times and the experimenter manually recorded the answer. If the subject failed or did not answer within 15 sec, the picture was presented again with the corresponding name written below it and the subject was asked to read the word aloud. The pair of stimuli remained on the screen until the subject either read the word or 40 sec elapsed. The subject never listen to the written word spoken aloud by someone else. To measure baseline performance, at the beginning of each week and before the training each subject was asked to name the pictures, one at a time, without help.

Both the experimenter and the patients were blinded regarding the different experimental conditions (anodic vs. sham).

Follow-up

At 1 week and 3 weeks after the training, for each stimulation condition two subjects were again shown the corresponding group of pictures and asked to name them without help. As before, the PC recorded vocal reaction times and the examiner manually recorded the answers. For personal reasons, Subject M. B. (Case 1) was unable to participate in the follow-up sessions.

Healthy Subjects

Data Analysis

For all subjects, the mean number of correctly recognized pairings in the verification phase was the same in all three experimental conditions (sham = 15, left anodic = 15, right anodic = 16).

Before beginning the word retrieval phase, the subjects were tested on each experimental list. No subject was able to name more than one picture (baseline performance). Furthermore, no subject learned the 20 experimental words in 35 min and, in the three conditions, all subjects responded to approximately the same number of item presentations in 35 min (left anodic, mean = 12.5, *SD* = 5.8; right anodic, mean = 11, *SD* = 7.1; sham, mean = 11.2, *SD* = 5.4).

For each tDCS condition, the mean number of correct responses and the mean vocal response time to each correct item were computed. Data analysis was performed with Statistica 6 software. Data were analyzed with repeated measure ANOVA with one within-subject condition factor (three levels: left anodic, right anodic, and sham).

Results

Accuracy. ANOVA showed that naming accuracy was unaffected by tDCS across the different conditions [left anodic, mean = 62%, *SD* = 30; right anodic, mean = 52%, *SD* = 38; sham, mean = 54%, *SD* = 27; $F(2, 18) < 1$, *ns*].

Vocal reaction times. The analysis revealed a significant condition effect [$F(2, 18) = 14.90$, $p < .0001$]. The Bonferroni-corrected Student's t test revealed that the mean vocal reaction time in the left anodic condition was significantly faster (mean = 1185 msec, *SD* = 318) than that in the sham condition (mean = 1495 msec, *SD* = 365; $p < .01$) and in the right anodic condition (mean = 1650 msec, *SD* = 458; $p < .0001$). The latter two conditions did not differ significantly from each other (*ns*) (see Figure 4).

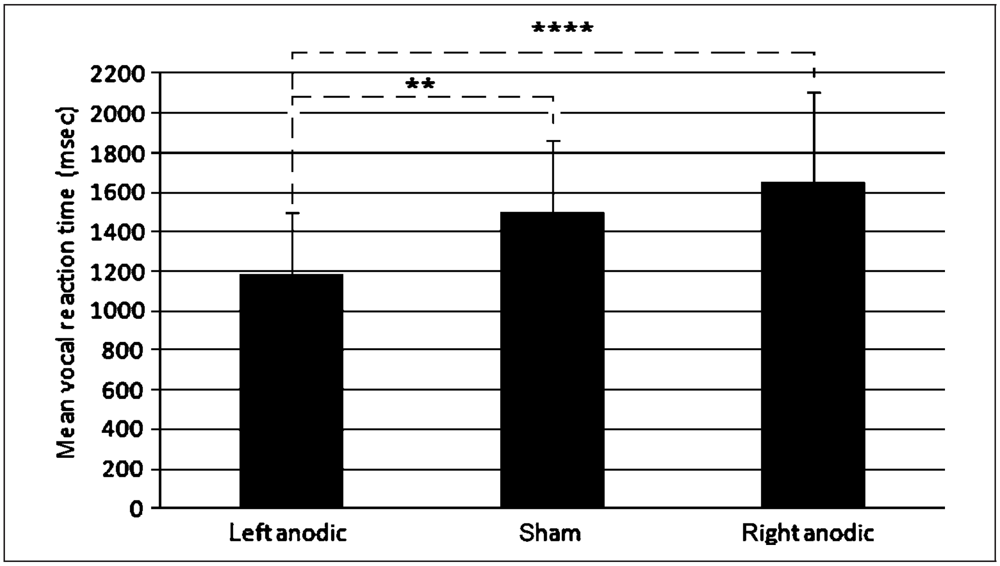

Figure 4. Effect of the tDCS on vocal reaction times of healthy subjects for the left anodic, sham, and right anodic conditions, respectively. $^{**}p < .01$; $^{****}p < .0001$.

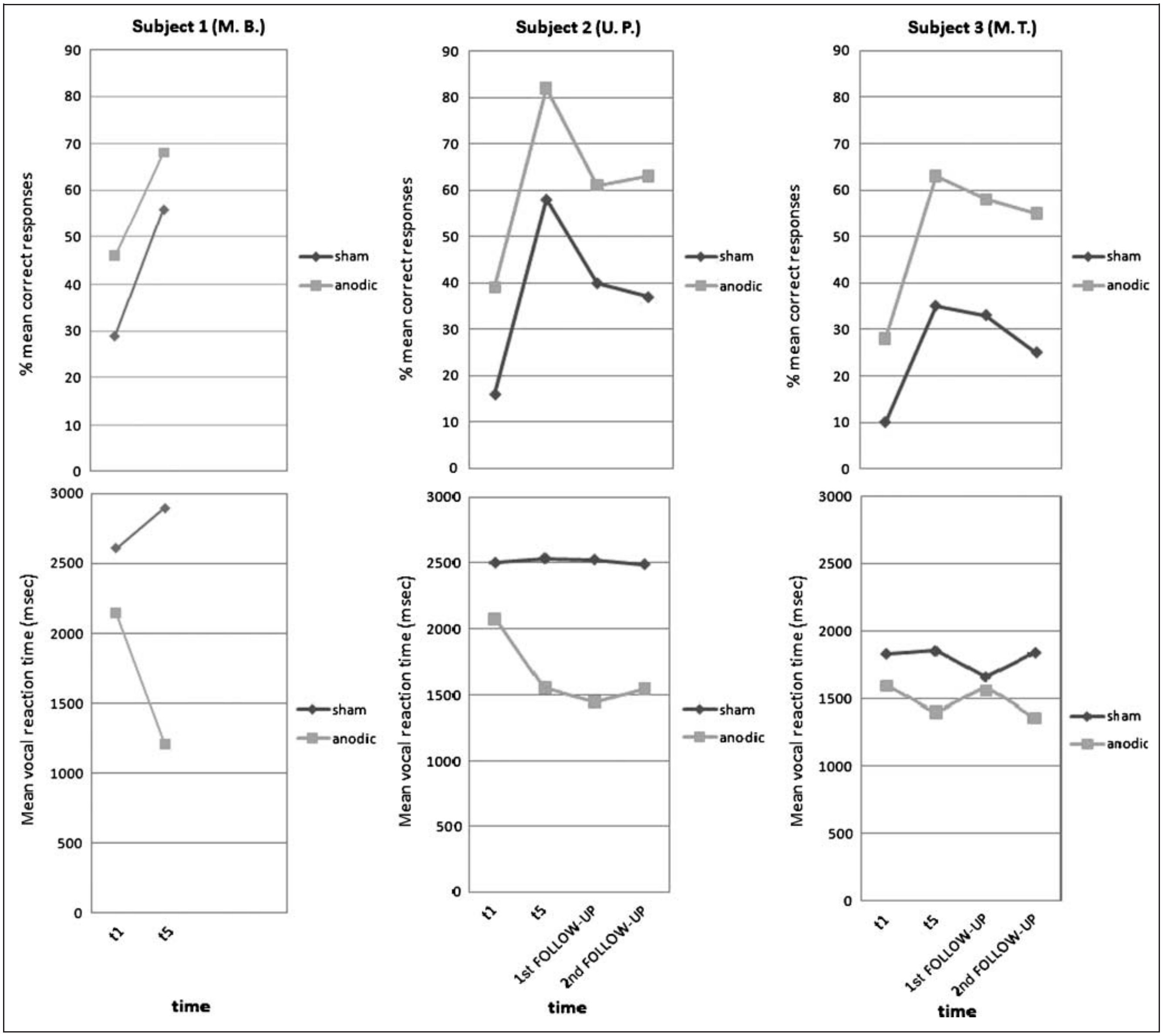

Figure 5. Percentage of correct responses and mean vocal reaction times for each subject as a function of condition (sham vs. anodic stimulation of left Wernicke's area) and time (t1 = first day, t5 = fifth day, first follow-up at 1 week posttreatment, second follow-up at 3 weeks posttreatment). Note that Case M. B. was not available for follow-up testing at 1 and 3 weeks posttreatment.

Comments. Data analysis clearly showed a beneficial effect of anodic stimulation over the left Wernicke's area when a group of healthy subjects learned novel words. Therefore, results seem to indicate that tDCS has a positive effect not only when subjects are required to recognize previously learned stimulus pairings as already demonstrated by Floel et al. (2008) but also when they have to retrieve their names. The finding of unaffected performances following anodic tDCS over the right hemisphere or following sham stimulation makes nonspecific effects (e.g., intersensory facilitation, arousal or enhancement of attention) unlikely and indicates the specificity of the effect over the left language area.

These data prompted us to use the same methodology with aphasic patients to see whether their anomic difficulties would improve. As already mentioned, these patients usually have word-finding difficulties due to their inability to find the "phonological word code" (Levelt & Meyer, 2000; Levelt et al., 1999).

Aphasic Subjects

Data Analysis

Prior to the training, no subject was able to name more than one picture in each experimental list (baseline performance).

First, for each patient, we conducted a descriptive analysis (see Figure 5) on mean percentage of response accuracy and mean vocal reaction time by type of condition

Table 2. Mean Percentage (±*SD*) of Correct Responses of Aphasic Subjects on the First and Fifth Days of Treatment in the Sham and Anodic Conditions, Respectively

Time	*Sham*	*Anodic*
t1	18 (±39)	38 (±49)
t5	50 (±50)	71 (±46)
Mean	34 (±47)	54 (±50)

(anodic vs. sham) and time. As shown in Figure 5, at the end of the treatment, all patients showed improved response accuracy and a decrease in vocal reaction time in the anodic condition with respect to the sham condition; moreover, in two patients, the effect persisted 3 weeks after the end of the training.

As the subject group was small, data were analyzed with a mixed effect model (Brysbaert, 2007; Baayen, Tweedie, & Schreuder, 2002), which allows controlling for item and subject variability. Two different analyses were performed: one for response accuracy (labeling each correct item 1 and each incorrect item as 0) and one for vocal reaction times to each item. For each analysis, two fixed factors were included, that is, *time* [two levels, first (t1) vs. fifth (t5) training day] and *condition* (two levels, anodic vs. sham); participant and item were entered in the analysis as random factors. Interaction was explored using Bonferroni's post hoc test.

Results

Accuracy. The analysis showed a significant effect of time [two levels, first (t1) vs. fifth (t5) training day, $F(1, 357) = 60.38$, $p < .0001$] and condition [$F(1, 304) = 22.18$, $p < .0001$]. Neither the interaction ($F < 1$) nor the random factors were significant. Subjects' performances significantly improved on the fifth day of training with respect to the first day [mean = 60%, *SD* = 49 (t5) vs. 28%, *SD* = 45 (t1); $p < .0001$]. Moreover, the mean number of correct responses was significantly greater in the anodic than in the sham condition (mean = 54%, *SD* = 50 vs. 34%, *SD* = 47, respectively; $p < .0001$) (see Table 2).

In other words, naming accuracy improved in the anodic (differences between t1 vs. t5 = 33%; $p < .0001$) and in the sham condition (differences between t1 vs. t5 = 32%, $p < .0001$). However, response accuracy was greater for the anodic than for the sham condition both on the first (differences between anodic vs. sham = 20%, $p < .001$) and the fifth day of treatment (differences between anodic vs. sham = 21%, $p < .001$) (see Figure 6 and Table 2).

Vocal reaction times. The analysis showed a significant effect for condition [$F(1, 198) = 8.81$, $p < .01$] but not for time [two levels, first (t1) vs. fifth (t5) training day, $F < 1$] or interaction ($F < 1$). No significant effects were found for the random factors. As shown in Figure 7, reaction times were significantly faster in the anodic than in the sham condition (mean = 1689 msec, *SD* = 1840 vs. 2508 msec, *SD* = 1934; $p < .01$.).

Note that although the analysis showed no significant interactions, Bonferroni's post hoc test revealed a significant decrease in response times from the first to the fifth day of training only for the anodic condition (mean = 1982 msec, *SD* = 1464 vs. 1396 msec, *SD* = 646, respectively; difference = 586 msec, $p < .01$; sham condition, mean = 2440 msec, *SD* = 1537 vs. 2576 msec, *SD* = 2861; difference = −136 msec, *ns*). Moreover, although on the first day vocal reaction times did not significantly differ between the two conditions (difference = −458 msec, *ns*), on the fifth day they were significantly shorter in the anodic than in the sham condition (differences between anodic vs. sham = 1180 msec, $p < .001$) (Table 3).

Comments. Similar to the results obtained in healthy subjects, the analysis showed that anodic stimulation had

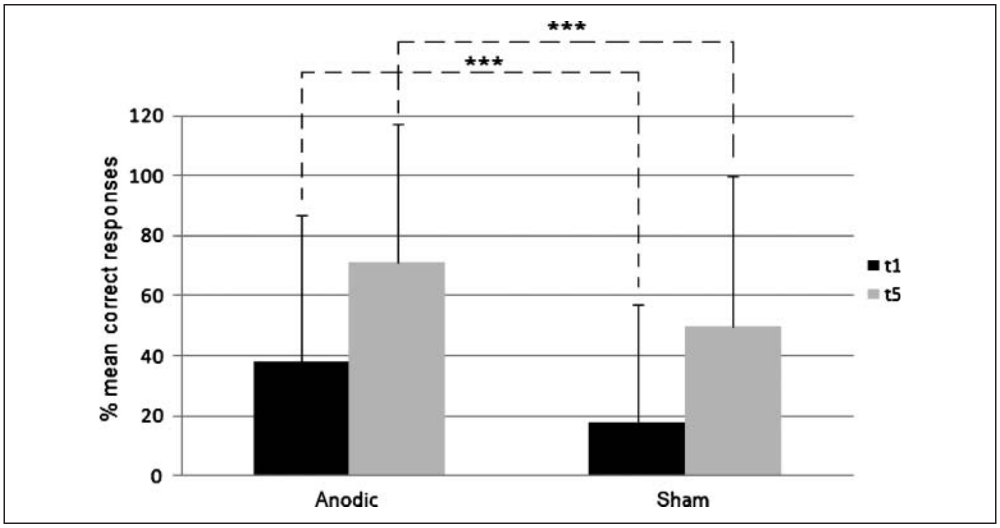

Figure 6. Mean percentage (±*SD*) of correct responses for aphasic subjects on the first and fifth days of treatment for the anodic and sham conditions, respectively. ***$p < .001$.

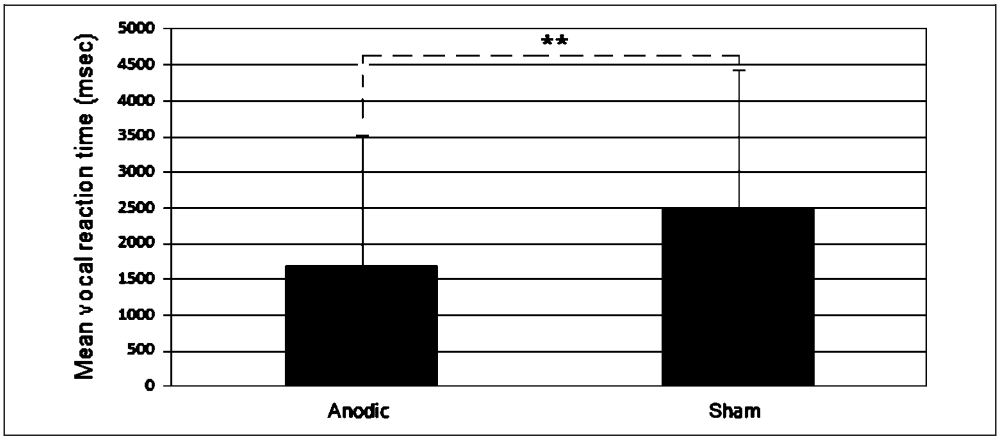

Figure 7. Mean vocal reaction times (±*SD*) of aphasic subjects for the anodic and sham conditions, respectively (**$p < .01$). For all patients, the RTs have been averaged across two time points [first (t1) and fifth (t5) training day].

a beneficial effect on the recovery of the aphasic subject's naming difficulties.

With regard to response accuracy, the patients' anomic disturbances were significantly improved at the end of the training in both conditions. This was because all three subjects underwent intensive language training in both conditions. In line with results of previous studies (Basso et al., 2001; Miceli et al., 1996; Howard et al., 1985), this anomia treatment alone brought about improvement. However, the beneficial effect of the anodic stimulation was evident because response accuracy was greater in this condition than in the sham condition. As has been observed in healthy subjects, vocal reaction times were faster in the anodic than in the sham condition. Moreover, the post hoc analysis revealed a significant reduction in response times between the first and the fifth day of treatment only for the anodic condition.

Follow-up

Data Analysis

Two aphasic subjects were retested 1 and 3 weeks after the end of treatment. For personal reasons, Subject M. B. (Case 1) was unable to participate in the follow-up sessions.

Data were analyzed using a mixed effect model, which allows controlling for item and subject variability. Two different analyses were conducted: one for response accuracy (labeling each correct item as 1 and each incorrect item as 0) and one for vocal reaction times. For each analysis, two within-subject factors were included: end-post treatment (three levels, fifth day vs. first follow-up vs. second follow-up) and condition (two levels, anodic vs. sham); participant and item were entered in the analysis as random factors. Interaction was explored using the Bonferroni's post hoc test.

Table 3. Mean (±*SD*) Vocal Reaction Times of Aphasic Subjects on the First and Fifth Days of Treatment for the Sham and Anodic Conditions, Respectively

Time	*Sham*	*Anodic*
t1	2440 (±1537)	1982 (±1464)
t5	2576 (±2861)	1396 (±646)
Mean	2508 (±1934)	1689 (±1840)

Results

Accuracy. The analysis showed a significant *end-post treatment* effect [$F(2, 340) = 4.48, p < .01$) and *condition* effect [$F(1, 241) = 29.69, p < .0001$]. Neither the interaction ($F < 1$) nor the random factors were significant.

Subjects' performances at the end of the treatment were significantly better than at the first and the second follow-up [59%, *SD* = 49 (t5) vs. 47%, *SD* = 50 (first follow-up), $p < .05$; 59.%, *SD* = 49 (t5) vs. 45%, *SD* = 50 (second follow-up), $p < .01$]; however, no significant differences were observed between the first and the second follow-up (mean = 47%, *SD* = 50 vs. 45%, *SD* = 50, respectively, *ns*). Furthermore, subjects' performances were more accurate in the anodic than in the sham condition (mean = 63%, *SD* = 48 vs. mean = 38%, *SD* = 49, respectively, $p < .0001$) (see Table 4).

Although no interaction was significant, post hoc analysis revealed greater response accuracy in the anodic than in the sham condition at the end of the treatment (difference

Table 4. Mean Percentage of Correct Responses (±*SD*) for Two Aphasic Subjects at the End of Treatment and at the First and Second Follow-up for the Sham and Anodic Conditions, Respectively

Time	*Sham*	*Anodic*	*Mean*
t5	46 (±50)	72 (±45)	59 (±49)
First follow-up	36 (±48)	59 (±50)	47 (±50)
Second follow-up	31 (±46)	59 (±50)	45 (±50)
Total Mean	38 (±49)	63 (±48)	

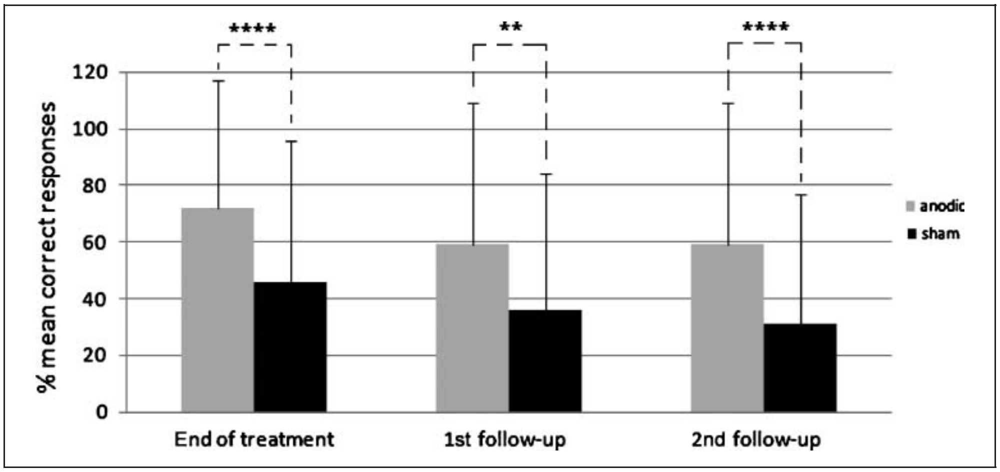

Figure 8. Mean percentage of correct responses of two aphasic subjects at the end of treatment and at the first and second follow-up for the anodic and sham conditions, respectively. $^{**}p < .01$; $^{****}p < .0001$.

anodic vs. sham. = 26%., $p < .0001$), at the first (difference anodic vs. sham = 23%, $p < .01$) and at the second follow up (difference anodic vs. sham = 28%, $p < .0001$) (see Figure 8 and Table 4).

Vocal reaction times. The analysis showed a significant condition effect [$F(1, 221) = 14.96$, $p < .0001$] but no end-post treatment ($F < 1$) effect or interaction effect ($F < 1$). Random factors were not significant. Mean vocal reaction times were significantly shorter in the anodic than in the sham condition (mean = 1486 msec, *SD* = 2006 vs. 2206 msec, *SD* = 1763; $p < .0001$). Moreover, the absence of a significant end-post treatment effect indicated that at 1 and 3 weeks after the end of treatment no significant effects were found for mean vocal reaction times (fifth day: 1886 msec, *SD* = 1817; first follow-up: 1822 msec, *SD* = 1723; second follow-up: 1830 msec, *SD* = 1752; *ns*). Finally, although the interaction was not significant, post hoc analysis revealed shorter response times in the anodic than in the sham condition, both at the end of treatment (difference anodic vs. sham = 850 msec, $p < .01$), at the first follow-up (difference anodic vs. sham = 602 msec, $p < .05$), and at the second follow-up (difference anodic vs. sham = 764 msec, $p < .05$) (see Figure 9).

In summary, although response accuracy decreased between the end of treatment and the two follow-up sessions, no further decrement was found between the first and the second follow-up. Moreover, analysis of reaction times revealed no significant changes 3 weeks after the end of treatment. Finally, response accuracy and naming latencies were always significantly better in the anodic than in the sham condition.

GENERAL DISCUSSION

The aim of this study was to determine whether anodic tDCS over the left Wernicke's area, together with concomitant language training, would bring about a significant improvement in novel word learning in healthy subjects and a recovery of anomic disturbances in left brain-damaged subjects.

Using a previously tested experimental anomic treatment paradigm (Basso et al., 2001), healthy subjects were asked to learn novel words (non words) associated with

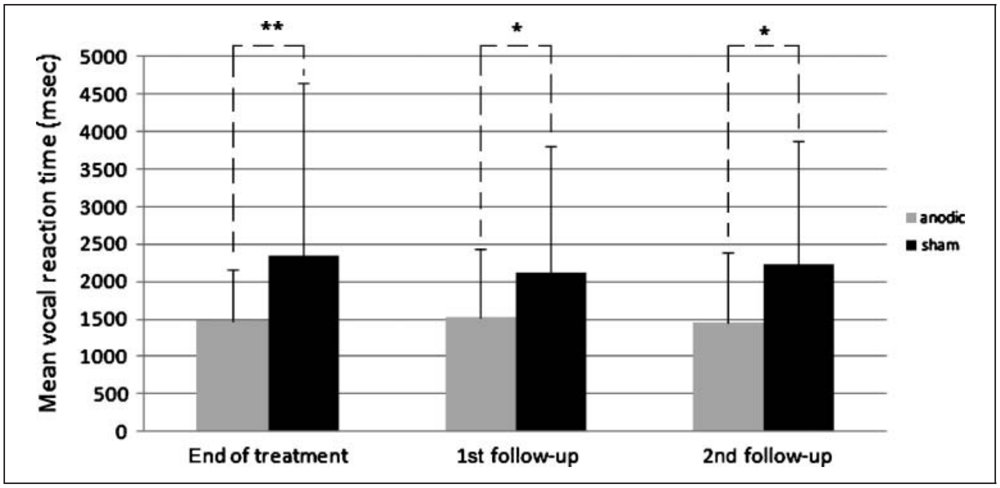

Figure 9. Mean vocal reaction times of two aphasic subjects at the end of treatment and at the first and second follow-up for the anodic and sham conditions, respectively. $^{*}p < .05$; $^{**}p < .01$.

pictures. In this condition, similarly to what is generally observed in anomic patients, the subjects were able to activate the complete semantic representation but could not activate the corresponding phonological form at the lexical level because, by definition, they had not yet learned it.

When we analyzed the healthy subjects' results in the three stimulation conditions (left anodic, right anodic, and sham), we found that left anodic stimulation led to a significant facilitation in picture naming with regard to vocal response times and not to naming accuracy. Moreover, the absence of a significant effect during the sham and the right anodic conditions allowed us to affirm that the results were specific to stimulation of the left language area. These results are in good accordance with those of previous tDCS studies in healthy subjects (Floel et al., 2008; Sparing et al., 2008). Using the same technique, Sparing et al. (2008) found faster naming latencies in a group of healthy subjects only after anodic stimulation of the left perisylvian region, including Wernicke's area (Sparing et al., 2008). Floel et al. (2008) reported similar results. They set out to determine whether tDCS over the left language area in a group of healthy subjects would have a positive influence on novel word learning and found enhanced performance only during the anodic stimulation of the left Wernicke's area.

In their study, beneficial effects were measured in terms of response accuracy and response times in recognizing new associations between the novel word and the word presented in the mother tongue and not in a naming condition. The new aspect of our results is that anodic tDCS of the temporal region (including Wernicke's area) improves performance not only during recognition of new words (Floel et al., 2008) but also during word retrieval.

These data are in line with previous rTMS and fMRI results suggesting a specific role of the temporal region during activation of phonological word representation in the late stages of lexical access (Yagishita et al., 2008; Kemeny et al., 2006; Mottaghy et al., 1999; Topper, Mottaghy, Brugmann, Noth, & Huber, 1998). Based on this finding, it was proposed in a meta-analysis that the left temporal region has a specific role in lexical–phonological retrieval (Indefrey & Levelt, 2000; see also Hickok & Poeppel, 2004).

Although, to date, the mechanisms underlying these beneficial effects are largely unknown, some authors have hypothesized that anodic stimulation elicits a prolonged increment in cortical excitability, probably due to depolarization of the neuronal membrane and changes in the synaptic connections of the *N*-methyl-D-aspartate (NMDA) receptors involved in long-term potentiation (Nitsche & Paulus, 2000, 2001).

In this study, we measured the positive effect (of anodic stimulation) on healthy subjects performing a word-naming task to make a direct comparison with aphasics. Although we are unable to draw any definitive conclusions from our results because of the small size of our patient group, data suggest that, in aphasic patients, anodic tDCS applied over Wernicke's area, together with simultaneous language training, leads to significantly improved performance on a naming task. Improvement was most evident in response times, which in two patients were still significantly faster for the anodic condition 3 weeks after the end of treatment. As already mentioned, as far as we know, only Monti et al.'s (2008) work has shown a positive effect of tDCS in the recovery of naming in chronic aphasia. However, these authors did not report data on the persistence of effects probably because, in their work, tDCS was applied in one session. Accordingly, in an rTMS study, Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al. (2005) found a significant improvement of naming difficulties in four chronic aphasics when stimulation was applied for 10 consecutive days. The effect still persisted at 2 months post-rtMS and, in three patients, lasting benefits were found at 8 months. In chronic patients, Kim et al. (2006) delivered TMS over the damaged motor cortex concomitantly with motor training and found that the paretic hand was improved. One plausible explanation advanced by the authors was that after stroke, the unaffected motor cortex might be disinhibited by the reduction in transcallosal inhibition from the affected motor cortex. This phenomenon leads to an increased interhemispheric inhibition of the affected motor cortex, which impedes motor recovery. The stimulation over the damaged motor area might have reduced the inhibition exerted by the contralateral unaffected hemisphere via the transcallosal pathway, leading to a better recovery (Kim et al., 2006). It would likely be the case that in our patient (M. T.), in which stimulation was directly delivered over the damaged areas, a similar mechanism took place. Thus, the abovementioned studies confirm the importance of associating stimulation with specific training.

In a recent review, Bolognini et al. (2009) suggested that uninjured tissue might be particularly receptive to modulation by various external tools including behavioral training and neuromodulatory approaches such as noninvasive tDCS of the brain. Given that these strategies have some similar mechanisms of action, that is, both induce similar changes in the neural excitability of the lesioned area, they might be more beneficial when used together. In fact, brain stimulation can prime cortical excitability, optimizing the learning processes involved in standard rehabilitation therapies and leading to more pronounced and long-term functional gains (Bolognini et al., 2009). The results obtained in the present study argue in favor of this hypothesis.

In conclusion, our results suggest that anodic tDCS applied over Wernicke's area enhances verbal learning in healthy individuals and might have an important effect on the recovery of language functions. Although these findings have to be considered preliminary because of the small size of our patient group, they might be useful for planning new therapeutic interventions in aphasia rehabilitation.

Acknowledgments

We thank the BIC staff at the Montreal Neurological Institute, McGill University, Canada, for providing us with software for brain image investigations. F. T. thanks the "Cassa di Risparmio di Volterra" for providing technical equipment and Dr. G. Mariani (General Manager) and G. Brunale (President) for their support in setting up the "Laboratory of Neuroanatomy" at the "Auxilium Vitae" Volterra (Pisa).

Reprint requests should be sent to Prof. Paola Marangolo, Department of Neuroscience, Faculty of Medicine, Ancona, Italy, or via e-mail: p.marangolo@univpm.it.

REFERENCES

Antal, A., Nitsche, M. A., Kincses, T. Z., Kruse, W., Hoffmann, K. P., & Paulus, W. (2004). Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. *European Journal of Neuroscience, 19,* 2888–2892.

Baayen, R. H., Tweedie, F. J., & Schreuder, R. (2002). The subjects as a simple random effect fallacy: Subject variability and morphological family effects in the mental lexicon. *Brain and Language, 81,* 55–65.

Basso, A., Marangolo, P., Piras, F., & Galluzzi, C. (2001). Acquisition of new "words" in normal subjects: A suggestion for the treatment of anomia. *Brain and Language, 77,* 45–59.

Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., et al. (2007). A randomized double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology, 11,* 1–6.

Bolognini, N., Pascual-Leone, A., & Fregni, F. (2009). Using non-invasive brain stimulation to augment motor training-induced plasticity. *Journal of NeuroEngineering and Rehabilitation, 6,* 8.

Brysbaert, M. (2007). *"The language-as-fixed-effect fallacy": Some simple SPSS solutions to a complex problem (Version 2.0)*. Royal Holloway, University of London.

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *Journal of Computerized Assistance Tomography, 18,* 192–205.

De Renzi, E., & Vignolo, L. A. (1962). The Token Test: A sensitive test to detect receptive disturbances in aphasia. *Brain, 85,* 665–678.

Di Lazzaro, V., Pilato, F., Di Leone, M., Proficue, P., Capone, F., Ranieri, F., et al. (2008). Modulating cortical excitability in acute stroke: A repetitive TMS study. *Clinical Neurophysiology, 119,* 715–723.

Ferrucci, R., Mameli, F., Guidi, I., Mrakic-Sposta, S., Vergari, M., Marceglia, S., et al. (2008). Transcranial direct current stimulation improves recognition memory in Alzheimer Disease. *Neurology, 71,* 493–498.

Floel, A., Rosser, N., Michka, O., Knecht, S., & Breitenstein, C. (2008). Non invasive brain stimulation improves language learning. *Journal of Cognitive Neuroscience, 8,* 1415–1422.

Fregni, F., Boggio, P. S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., et al. (2005). Anodal transcranial current stimulation of prefrontal cortex enhances working memory. *Experimental Brain Research, 166,* 23–30.

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.

Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition, 92,* 67–99.

Howard, D., Patterson, K., Franklin, S., Orchardlisle, V., & Morton, J. (1985). The facilitation of picture naming in aphasia. *Cognitive Neuropsychology, 2,* 49–80.

Indefrey, P., & Levelt, W. J. M. (2000). The neural correlates of language production. In M. Gazzaniga (Ed.), *The new cognitive neurosciences* (2nd ed., pp. 845–865). Cambridge, MA: MIT Press.

Iyer, M. B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., & Wassermann, E. M. (2005). Safety and cognitive effects of frontal DC brain polarization in healthy individuals. *Neurology, 64,* 872–875.

Jennum, P., Friberg, L., Fuglsang-Frederiksen, A., & Dam, M. (1994). Speech localization using repetitive transcranial magnetic stimulation. *Neurology, 44,* 269–273.

Kemeny, S., Xu, J., Park, G., Hosey, L., Wettig, C., & Braun, A. (2006). Temporal dissociation of early lexical access and articulation using a delayed naming task: An fMRI study. *Cerebral Cortex, 16,* 587–595.

Kikyo, H., Ohki, K., & Miyashita, Y. (2002). Neural correlates for feeling-of knowing: An fMRI parametric analysis. *Neuron, 36,* 177–186.

Kikyo, H., Ohki, K., & Sekihara, K. (2001). Temporal characterization of memory retrieval processes: An fMRI study of the "tip of the tongue" phenomenon. *European Journal of Neuroscience, 14,* 887–892.

Kim, Y. H., You, S. H., Ko, M. H., Park, J. W., Kwang, H. L., Jang, S. H., et al. (2006). Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke, 37,* 1471–1476.

Levelt, W. J. M. (1992). Accessing words in speech production: Stages, processes and representations. *Cognition, 42,* 1–22.

Levelt, W. J. M., & Meyer, A. S. (2000). Word for word: Multiple lexical access in speech production. *European Journal of Cognitive Psychology, 12,* 433–452.

Levelt, W. J. M., Roelofs, A., & Meyer, A. S. (1999). A theory of lexical access in speech production. *Behavioral and Brain Sciences, 22,* 1–75.

Miceli, G., Amitrano, A., Capasso, R., & Caramazza, A. (1996). The treatment of anomia resulting from output lexical damage: Analysis of two cases. *Brain and Language, 52,* 150–174.

Miceli, G., Laudanna, A., Burani, C., & Capasso, R. (1994). *Batteria per l'analisi dei deficit afasici BADA*. Rome: CEPSAG, Policlinico Gemelli, Università Cattolica del Sacro Cuore.

Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, F., Mameli, F., Mrakic-Sposta, S., et al. (2008). Improved naming after transcranial direct current stimulation in aphasia. *Journal of Neurology, Neurosurgery and Psychiatry, 79,* 451–453.

Mottaghy, F. M., Huber, W., Brugmann, M., Sparing, R., Boroojerdi, B., Foltys, H., et al. (1999). Facilitation of picture naming after transcranial magnetic stimulation. *Neurology, 53,* 1806–1812.

Mrakic-Sposta, S., Marceglia, S., Mameli, F., Dilena, R., Tadini, L., & Priori, A. (2008). Transcranial direct current stimulation in two patients with Tourette Syndrome. *Movement Disorders, 15,* 2259–2261.

Naeser, M. A., Martin, P. I., Nicholas, M., Baker, E. H., Seekins, H., Helm-Estabrooks, N., et al. (2005). Improved naming after TMS treatments in a chronic, global aphasia patient: Case report. *Neurocase, 11,* 182–193.

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.

Naeser, M. A., Palumbo, C. L., Helm-Estabrooks, N., Stiassny-Eder, D., & Albert, M. L. (1989). Severe non-fluency in aphasia: Role of the medial subcallosal fasciculus plus other white matter pathways in recovery of spontaneous speech. *Brain, 112,* 1–38.

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

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57,* 1899–1901.

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., et al. (2003). Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *Journal of Cognitive Neuroscience, 15,* 619–626.

Novak, D. A., Grefkes, C., Dafotakis, M., Eickoff, S., Kust, J., Karbe, H., et al. (2008). Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Archives of Neurology, 65,* 741–747.

Olivieri, M., Rossini, P. M., Traversa, R., Cicinelli, P., Filippi, M. M., Pasqualetti, P., et al. (1999). Left frontal transcranial magnetic stimulation reduces contralesional extinction in patients with unilateral right brain damage. *Brain, 122,* 1731–1739.

Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., & Vallar, G. (1987). Verbal and spatial immediate memory span: Normative data from 1355 adults and 1112 children. *Italian Journal of Neurological Sciences, 8,* 537–548.

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

Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory, 6,* 174–215.

Sparing, R., Dafotakis, M., Meister, I. G., Thirugnanasambandam, N., & Fink, G. R. (2008). Enhancing language performance with non-invasive brain stimulation: A transcranial direct current stimulation study in healthy humans. *Neuropsychologia, 46,* 261–268.

Topper, R., Mottaghy, F. M., Brugmann, M., Noth, J., & Huber, W. (1998). Facilitation of picture naming by focal transcranial magnetic stimulation of Wernicke's area. *Experimental Brain Research, 121,* 371–378.

Watanabe, T., Yagishita, S., & Kikyo, H. (2008). Memory of music: Roles of right hippocampus and left inferior frontal gyrus. *Neuroimage, 39,* 483–491.

Yagishita, S., Watanabe, T., Asari, T., Ito, H., Kato, M., Ikehira, H., et al. (2008). Role of left superior temporal gyrus during name recall process: An event-related fMRI study. *Neuroimage, 41,* 1142–1153.

Zimmermann, P., & Fimm, B. (1994). *Tests d'évaluation de l'attention (TEA)*. Freiburg: Psytest.