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Enhancing language performance with non-invasive brain stimulation—A transcranial direct current stimulation study in healthy humans

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Abstract

In humans, transcranial direct current stimulation (tDCS) can be used to induce, depending on polarity, increases or decreases of cortical excitability by polarization of the underlying brain tissue. Cognitive enhancement as a result of tDCS has been reported. The purpose of this study was to test whether weak tDCS (current density, 57 $\mu A/cm^2$) can be used to modify language processing. Fifteen healthy subjects performed a visual picture naming task before, during and after tDCS applied over the posterior perisylvian region (PPR), i.e. an area which includes Wernicke's area [BA 22]. Four different sessions were carried out: (1) anodal and (2) cathodal stimulation of left PPR and, for control, (3) anodal stimulation of the homologous region of the right hemisphere and (4) sham stimulation. We found that subjects responded significantly faster following anodal tDCS to the left PPR ($p < 0.01$). No decreases in performance were detected. Our finding of a transient improvement in a language task following the application of tDCS together with previous studies which investigated the modulation of picture naming latency by transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS) suggest that tDCS applied to the left PPR (including Wernicke's area [BA 22]) can be used to enhance language processing in healthy subjects. Whether this safe, low cost, and easy to use brain stimulation technique can be used to ameliorate deficits of picture naming in aphasic patients needs further investigations.

Keywords: tDCS; Brain polarization; Electrical stimulation; Naming; Linguistic processing; Speech

1. Introduction

Recently, the manipulation of cognitive functions by non-invasive stimulation of the human brain gains increasing attention. Several studies of healthy or brain-damaged patients suggest that transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS) can be used to non-invasively excite or inhibit cortical areas (for recent reviews see, e.g., Hummel & Cohen, 2006; Talelli & Rothwell, 2006). Sustained suppression of excitability is achieved, for example, if rTMS is applied at low frequencies (up to 1 Hz), also known as the "virtual-lesion approach", since behavioural deficits can be induced which resemble those observed following a stroke (Pascual-Leone, Bartres-Faz, & Keenan, 1999). Less frequently, an enhancement of cognitive performance has been reported, mostly following high-frequency rTMS in both healthy subjects (e.g., Boroojerdi et al., 2001; Mottaghy et al., 1999) and patients (e.g., in depression, Moser et al., 2002).

However, cognitive functions might be modulated more effectively by a recently revived neuromodulatory technique: transcranial direct current stimulation (tDCS) (Hummel & Cohen, 2006; Paulus, 2004; Talelli & Rothwell, 2006). During tDCS, weak polarizing direct currents are delivered to the cor-

Abbreviations: BA, Brodmann'ms area; PET, positron emission tomography; PPR, posterior perisylvian region; rTMS, repetitive transcranial magnetic stimulation; STG, superior temporal gyrus; tDCS, transcranial direct current stimulation

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tex via two electrodes placed on the scalp. TDCS of the motor cortex has been shown to induce long-lasting changes in cortical excitability (Nitsche & Paulus, 2000; Nitsche et al., 2005). The nature of these effects depends strongly on the polarity of the current, i.e., if the anode is placed over the motor cortex with the cathode above the contralateral orbit being the reference electrode, motor cortex excitability increases, and vice versa. Enhancement of cognitive functions by means of tDCS has been demonstrated in healthy subjects for higher motor functions (Antal et al., 2004), auditory memory (Vines, Schnider, & Schlaug, 2006), working memory (Fregni et al., 2005), memory consolidation during sleep (Marshall, Molle, Hallschmid, & Born, 2004) and learning (Kincses, Antal, Nitsche, Bartfai, & Paulus, 2004; Nitsche et al., 2003c). Unlike TMS, tDCS does not induce direct neuronal depolarisation. There is increasing evidence that it acts upon the resting membrane potential through the modulation of sodium and calcium-dependent channels and NMDA-receptor activity, thereby promoting LTP/LTD-like mechanisms (e.g., Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2004).

Though TMS has been reported to facilitate many language-related tasks, including semantic processing (Andoh et al., 2006), word associations (Bridgers et al., 1989), digit span (Duzel, Hufnagel, Helmstaedter, & Elger, 1996), and, in particular, picture naming (Cappa, Sandrini, Rossini, Sosta, & Miniussi, 2002; Mottaghy et al., 1999; Sparing et al., 2001; Töpper, Mottaghy, Brügmann, Noth, & Huber, 1998; Wassermann et al., 1999), enhancement of language processes through tDCS has not yet been demonstrated. Furthermore, the relationship between the behavioural effects induced by both stimulation techniques remains unclear. In the present study we, therefore, used a simple picture naming task which has been investigated previously in a series of experiments with single-pulse TMS as well as rTMS (for a review, see, e.g., Mottaghy, Sparing, & Töpper, 2006). Based on these prior studies (Mottaghy et al., 1999; Sparing et al., 2001; Töpper et al., 1998) we expected to observe that tDCS applied over the left posterior perisylvian region (PPR) including Wernicke's area (Brodmann's area (BA) 22) enhances performance in a picture naming task.

2. Methods and materials

2.1. Subjects

Fifteen healthy subjects (5 female, mean age 26.9 ± 3.7 years) without any history of implanted metal objects, seizures or any other neurological disease participated in the experiments. All individuals were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) and native German speakers. The study was approved by the local ethics committee and all subjects gave written informed consent.

2.2. Transcranial direct current stimulation (tDCS)

tDCS was delivered by a battery driven, constant current stimulator (neuroConn GmbH, Ilmenau, Germany) using a pair of surface saline-soaked sponge electrodes (5 cm × 7 cm). A constant current of 2 mA intensity was applied for 7 min resulting in a current density of 57 $\mu A/cm^2$ at the skin. If applied according to present safety guidelines, tDCS is considered to be a safe brain stimulation technique associated with relatively minor adverse effects (Nitsche et al., 2003b; Poreisz, Boros, Antal, & Paulus, 2007). Two different electrode montages were used: the first electrode (to which polarity refers) was placed over CP5 of the extended International 10–20 system for EEG electrode placement. This site has been proven to correspond best with the location of Wernicke's area, including the posterior part of the left superior temporal gyrus (STG) (Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994) and has been used in a number of previous TMS studies (e.g., Knecht et al., 2002; Mottaghy et al., 1999). The homologous area of the right hemisphere was stimulated over CP6.

In general, the magnitude of the tDCS elicited changes in cortical excitability depends upon electrode montage due to the interdependence between neuronal orientation and the injected current densities orientation (e.g., Nitsche & Paulus, 2000; Wagner et al., 2007). At present, different electrode arrangements have been evaluated far more consistently for stimulation of the primary motor cortex than for non-motor areas. At the motor cortex, optimal results are achieved with one electrode placed over the primary motor cortex, and the other electrode fixed contralaterally above the right orbita (Nitsche & Paulus, 2000). Since there is no data available concerning the optimal electrode montage for stimulation of the PPR, we initially adopted the placement of the reference electrode from the classical electrode montage for stimulation of the primary motor cortex, i.e., the reference electrode was placed contralaterally over the frontopolar cortex. However, using this montage, we did not observed any differences between anodal and cathodal tDCS applied over CP5 in a group of four subjects. The results of this pilot experiment have, however, to be interpreted carefully due to the small sample size. Nevertheless, this montage was abandoned subsequently and the reference electrode was placed over Cz instead.

Overall, four different stimulation sessions were carried out: (1) anodal (CP5-A) and (2) cathodal (CP5-C) stimulation of left PPR and, for control, (3) anodal stimulation of the homologous region on the right hemisphere (CP6-A) and (4) sham stimulation (CP5-S). Sham stimulation was performed in the same way as stimulation of the left PPR; however, the stimulator was turned off after 30 s. In principle, the application of tDCS is associated with minimal to no somatosensory input that could confound both behavioural and sham conditions. Nevertheless, some subjects feel the electrical current as an itching sensation beneath both electrodes during the early rising phase of the direct current, i.e., during the first few seconds of stimulation. Our sham protocol ensured that subjects could feel the initial itching sensation at the beginning of tDCS, but prevented any effective modulation of cortical excitability by tDCS. It has been shown that such procedures allow successful blinding of subjects for the respective stimulation condition (Gandiga, Hummel, & Cohen, 2006). The stimulation sessions were separated by at least four hours. The order of sessions was varied systematically across subjects to control for learning effects, to avoid carry-over effects, and to guarantee a sufficient washout of the effects of the previous run, respectively. There have been no reports of behavioural performance effects lasting longer than 30 min subsequent to tDCS, however, changes of motor cortex excitability have been found to last up to 60 min or longer (Vines et al., 2006).

2.3. Task

The details of the experimental task have been described elsewhere (Mottaghy et al., 1999; Sparing et al., 2001). In brief, subjects were instructed to name as quickly as possible black-and-white line drawings of everyday objects presented on a PC monitor (screen size 53 cm, viewing distance 1 m). Pictures were presented for 1000 ms followed by a blank screen interval of 500 ms. Verbal responses were recorded by a microphone attached to the subject's collar and digitized for later offline analysis (16-bit resolution, sampling rate 22 kHz). Ten different objects that had proved to have the smallest standard deviations in naming latency across individuals (Töpper et al., 1998) were selected from a set of 260 pictures standardized for frequency and visual complexity (Snodgrass & Vanderwart, 1980). All words were 1–2 syllables in length and had different initial phonemes. Since the naming latency of an object decreases when the object is shown several times (Mitchell & Brown, 1988), the naming of the selected pictures was sufficiently overtrained by presenting each picture eight times before the main experiment. The total set of stimulus pictures used in each session contained two copies of each picture, i.e., 20 items. The order of items was randomized.

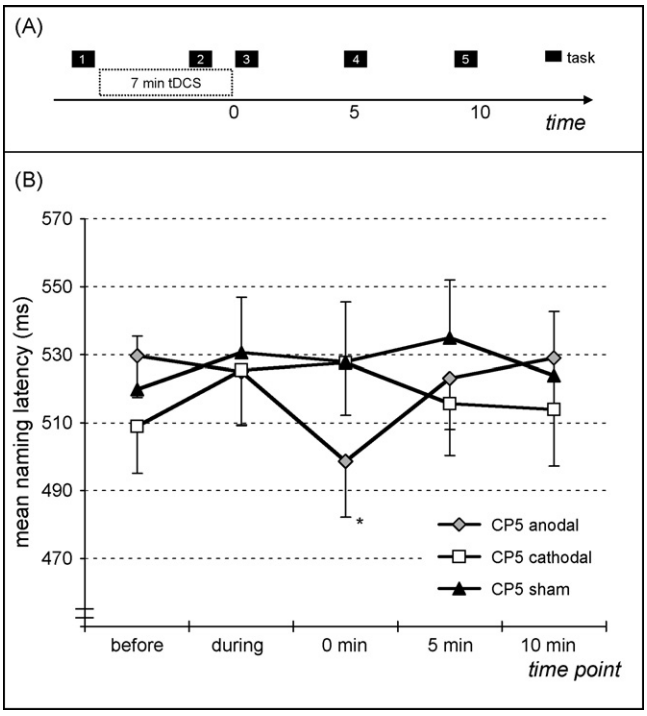

Fig. 1. Upper part (A): schematic timeline of the experimental procedure. In each of the four sessions, subjects performed the picture naming task before, during (i.e., after the fifth minute of tDCS), directly after or after the 5th and 10th minute following the cessation of tDCS, respectively. The session order was systematically counterbalanced across subjects. *Lower part (B)*: Results of tDCS over CP5 (i.e., the left posterior perisylvian region). Mean naming latencies over all subjects ($n = 15$) are shown for each stimulation condition (anodal, cathodal and sham) and for each time point. As main result, a significant decrease of naming latency was found directly after the end of anodal tDCS (0 min). Bars indicate standard errors (S.E.). $^*p < 0.01$.

2.4. Procedure

In each session, participants were required to perform the task, i.e., naming of the complete set of 20 pictures, five times: before tDCS, immediately after tDCS, and after the 5th and 10th minute following the cessation of tDCS (Fig. 1A). In addition, subjects performed the task while tDCS was applied, i.e., after the fifth minute of tDCS. Before each experimental trial, there were four warm-up trials. TDCS was applied either at CP5 (anodal: CP5-A; cathodal: CP5-C; sham: CP5-S) or at CP6 (anodal: CP6-A).

2.5. Analysis

An investigator blinded for the respective stimulation condition measured the latencies of the verbal responses using the recorded speech envelopes. To determine the exact acoustic onset, an amplitude filter was used that removed all acoustic signals with amplitudes less than 7.5% of the maximum sound level. Semantically incorrect responses, as well as responses that were, for instance, preceded by verbal searching or "tip-of-the-tongue" phenomena were excluded. Extreme delay was defined as a naming latency for a particular picture which exceeded the average naming latency by more than 2 S.D.s. Data were analyzed with repeated measure analysis of variance (ANOVA). ANOVA comprised the within-subject factors CONDITION [four levels] and TIME POINT [five levels], as well as gender as the between-subjects factor. Mauchly's test examined sphericity in the ANOVA model. We applied Duncan's multiple range test to compute *post hoc* comparisons. Differences were considered significant at a level of $p < 0.05$, for non-spherical data the Greenhouse–Geisser correction was used. All statistical analyses were performed using SPSS 12 for Windows software package.

3. Results

All subjects tolerated the treatment without any side effects. Their forced guessing concerning the difference between active and sham stimulation was at chance level. Accuracy of naming was unaffected by tDCS across the different conditions. Approximately 4% of the items had to be excluded. ANOVA showed no main effect for CONDITION ($F(3, 39) = 1.06$, $p = 0.38$) or TIME POINT ($F(4, 52) = 1.37$, $p = 0.26$), but yielded a significant interaction between both factors ($F(12, 156) = 3.39$, $p < 0.01$, Greenhouse–Geisser corrected). No significant effect of gender was observed ($F(1, 13) = 0.92$, $p = 0.36$). The mean naming latencies of the baseline conditions dependent upon the point of subsequent stimulation, i.e., naming before stimulation, did not differ significantly from each other (CP5-A 530 ± 47 ms S.D. (standard deviation), CP5-C 509 ± 54 ms, CP5-S 520 ± 60 ms and CP6-A 516 ± 59 ms, $p > 0.14$).

The calculation of *post hoc* contrasts using Duncan's test revealed that the participants responded significantly faster directly after the cessation of anodal tDCS applied over CP5 (499 ± 64 ms) compared to the corresponding time point after cathodal tDCS applied over CP5 (528 ± 59 ms) or sham stimulation (528 ± 68 ms) ($p < 0.01$) (Fig. 1B). These differences constitute a relative improvement in performance of approximately 6% and were present in the majority of subjects. The individual variances in naming latencies are shown for each single subject in Fig. 2.

When anodal tDCS was performed over the contralateral homologue of PPR (CP6), picture naming latency was higher compared to the stimulation of the speech-dominant (i.e., left) hemisphere (CP6-A 520 ± 60 ms vs. CP5-A 499 ± 64 ms) ($p < 0.02$) (Fig. 3).

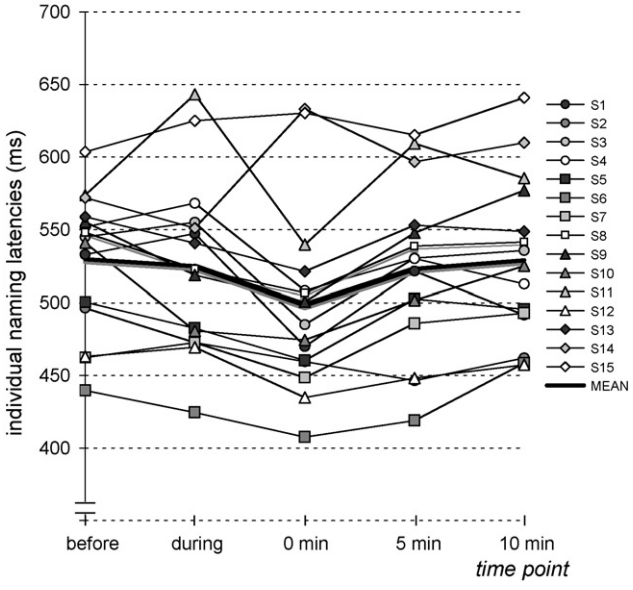

Fig. 2. Individual mean naming latencies following anodal tDCS applied to the left posterior perisylvian region (CP5) for each single subject (S, S1–S15) to illustrate the overall low variability in individuals.

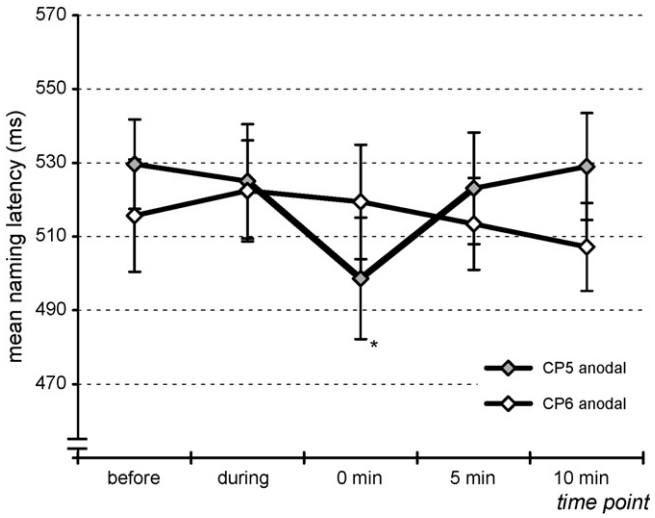

Fig. 3. Mean naming latencies for anodal tDCS to the left posterior perisylvian region (CP5) and to the homologue area of the right hemisphere (CP6). A significant facilitation of naming latency was only observed following the stimulation of the speech-dominant (i.e., left) hemisphere. Bars indicate standard errors (S.E.). *$p < 0.05$.

Table 1
Group mean naming latencies for each condition and time point

Condition	Before	During	0 min	5 min	10 min
CP5 anodal	530 ± 12	525 ± 16	499 ± 17	523 ± 15	529 ± 14
CP5 cathodal	509 ± 14	525 ± 16	528 ± 15	516 ± 15	514 ± 17
CP5 sham	520 ± 16	531 ± 16	528 ± 18	535 ± 17	524 ± 19
CP6 anodal	516 ± 15	522 ± 14	519 ± 15	513 ± 12	507 ± 12

Mean ± S.E.M.

In contrast, facilitation of naming latency was no longer observed at the latter time points of the session, i.e., 5 or 10 min after the end of tDCS (523 ± 58 ms and 529 ± 55 ms; $p > 0.58$). Furthermore, no other naming latency differences between other stimulation conditions reached significance, which means that in the current study no tDCS induced decreases in performance were detected (for group naming latencies, see Table 1).

4. Discussion

In the present experiment we demonstrated improvement in a language task following the application of anodal tDCS over the left PPR, i.e., an area which includes Wernicke's area [BA 22]. Stimulation resulted in a significant short-lasting facilitation of picture naming. The findings of an unaffected performance following anodal tDCS over the non-dominant hemisphere or following sham stimulation over PPR make unspecific effects, e.g., intersensory facilitation, arousal or enhancement of attention unlikely. Furthermore, practice-induced effects can be ruled out due to the fact that latencies returned to the baseline level after 5 and 10 min, respectively.

4.1. Effects of anodal tDCS on naming latency

Our finding that anodal tDCS applied over the left PPR speeds-up responses in healthy volunteers is in good accordance with prior TMS studies: Single-pulse TMS facilitates naming when it precedes object presentation by 500 or 1000 ms (Töpper et al., 1998). High-frequency rTMS (i.e., 20 Hz) has been proven to shorten naming latencies immediately after the cessation of rTMS (Mottaghy et al., 1999), whereas the facilitating effect of rTMS disappeared when the same amount of TMS stimuli was given at 1 Hz (Sparing et al., 2001). The modulation following 20 Hz-rTMS was somewhat larger than the tDCS induced modulation observed in our current study (relative change rTMS: 7–8% vs. anodal tDCS: 5–6%). At first sight, the changes resulting from such external neuromodulation may seem rather small. This could, at least in part, result from the fact (1) that naming of everyday-life objects is probably already highly, albeit not entirely optimized in healthy subjects and (2) that it was over-trained prior to testing to avoid learning effects during the sessions. It is conceivable that a less overtrained or even a novel task might be associated with more prominent changes in performance. However, in such situations higher individual variabilities might interfere with statistical evaluation. This issue needs further investigation.

Using rTMS, Andoh et al. (2006) reported an approx. three times larger reduction of reaction times in a language-fragment-detection task. Wassermann et al. (1999) achieved much larger decreases in naming latency, however, in their study temporal-lobe epilepsy patients were investigated and a different, presumably stronger, rTMS protocol was used. In the current study, we targeted at a principal language area. TDCS to other brain areas may also improve language tasks. Recently, a study on safety and cognitive side-effects of tDCS found improved verbal fluency following tDCS to the frontal lobe (Iyer, Schleper, & Wassermann, 2003).

Our results suggest that both stimulation techniques, i.e., anodal tDCS and high-frequency rTMS, if applied over PPR including Wernicke's area, act in the same direction although their induced (after-) effects on cortical excitability are probably based on different physiological mechanisms. Each single TMS pulse of an rTMS train basically induces a very brief electrical current in the stimulated brain tissue, which activates primarily the axons of cortical neurons. In contrast, anodal tDCS polarizes neuronal tissue through a weak constant electric field during the whole period of stimulation without induction of neuronal firing. Consequently, the excitatory effect of anodal tDCS is thought to result from a depolarizing shift of membrane potentials and a modulation of the spontaneous neuronal firing rate (Nitsche & Paulus, 2000; Paulus, 2003). The results of neuropharmacological studies suggest that one of its core mechanism might be the modulation of sodium and calcium-dependent channels and NMDA-receptor activity, promoting LTP/LTD-like mechanisms (e.g., Liebetanz et al., 2002; Nitsche et al., 2004).

4.2. No effects of cathodal tDCS on naming latency

In contrast to previous studies that reported clear-cut opposite effects of anodal and cathodal tDCS on cortical excitability (Nitsche & Paulus, 2000; Nitsche et al., 2005), we did not observe any significant influence of cathodal tDCS over CP5 on naming task performance. Since tDCS over the pri-

mary motor cortex is supposed to increase (cathodal tDCS) or decrease (anodal tDCS) cortical inhibition in the motor system, an increase in error rate or reaction time would have been expected following cathodal tDCS. Interestingly, this lack of a significant effect matches previous findings of studies applying low-frequency rTMS to Wernicke's area in language tasks (Sparing et al., 2001). The application of low-frequency rTMS usually leads to a lasting suppression of cortical excitability and has been used to investigate brain-behaviour relationships via so-called "virtual lesions" (Pascual-Leone et al., 1999). It is noteworthy, that there has been no TMS study so far that reported inhibitory effects in a visual picture naming task resulting from TMS to the PPR. However, short trains of high-frequency (10 Hz) rTMS compromise naming when applied to left inferior temporal cortex (BA 37) (Stewart, Meyer, Frith, & Rothwell, 2001). In a picture-word verification task, Knecht et al. (2002) could also demonstrate that low-frequency rTMS to the left STG suppresses performance depending upon the lateralization of language. Interestingly, a recent study has questioned the general validity of the assumption that low-frequency rTMS impairs task performance as a result of reduced cortical excitability. Andoh et al. (2006) observed that 1 Hz-rTMS over Wernicke's area did not increase reaction times as expected, but enhanced performance in a language fragment-detection task.

4.3. General remarks and possible limitations

The interpretation of our experimental results could be limited by the fact that each brain area responsive to stimulation is, in general, actually a window onto a large-scale functional network, rather than an isolated site (Manjaly et al., 2005; McIntosh, 2000). The ability to name visually presented objects represents a complex cognitive process, decomposable into various components (e.g., recognition of the stimulus, access to its meaning, access to the corresponding phonological word from, as well as motor programming and articulation). Functional imaging and lesion studies in stroke patients revealed a number of distinct and/or interacting brain areas to underlie these components: left anterior, inferior, and posterior middle/superior temporal cortex and fusiform gyri (including BA 37), posterior inferior frontal, inferior parietal cortex and primary visual cortex (for a recent review, see, e.g., DeLeon et al., 2007). Therefore, it is impossible to differentiate whether anodal tDCS acts primarily through a local modulation of excitability of the left PPR, or whether it affects a larger language network as a whole. Anodal tDCS applied to the left PPR, including Wernicke's area, may lead to a "preactivating" synchronization of neuronal networks involved primarily in lexical-semantic search. As a result, the processing and throughput within this network might be enhanced. In contrast, tDCS may also act upon a larger network of interconnected brain areas involved in naming. Indeed, remote effects of brain stimulation have been reported in studies combining both rTMS and tDCS with neuroimaging techniques, respectively (see below).

Another important limitation of tDCS is its relatively low spatial focality due to (1) large tDCS electrode sizes (e.g., 35 cm^2) and (2) the fact that the reference electrode may cause confounding stimulation effects. However, recent data from computer-based modelling of current density distributions suggest that the direct functional effects of tDCS result from stimulation of the area under the electrode and, moreover, that the current density magnitude decreases rapidly with distance from it (Miranda, Lomarev, & Hallett, 2006; Wagner et al., 2007). These findings are supported by tDCS experiments in humans. For instance, changing the position of the stimulation electrode a few centimeters alters its efficacy (Nitsche et al., 2003a,b,c). In future studies, more selective effects of the active electrode may be achieved by increasing the size of the reference electrode. Such a procedure can result in a functionally inefficient reference electrode (Nitsche et al., 2007).

The results of our experiment are in line with previous findings of rTMS studies which targeted the same cortical area to investigate picture naming tasks (see Table 2), although the spatial resolution of rTMS (10–20 mm) is lower compared to tDCS. Taken together, the similar results of both techniques suggest that the facilitation of naming latency following tDCS is the result of a specific effect exerted on the area under the electrode, i.e., the left PPR.

Nevertheless, it has also to be taken into account that functional imaging studies have proven that brain stimulation techniques such as TMS may exert local effects as well as remote changes in functionally connected brain regions (e.g., Paus et al., 1997). Unlike TMS, tDCS does not initiate action potentials due to the low current density magnitudes (Wagner et al., 2007). In fact, tDCS is thought to induce alterations in cortical excitability through hyperpolarizing and depolarizing shifts in the resting membrane potential. Using PET, Lang et al. (2005) reported widespread changes in blood flow following tDCS of the motor cortex. At first sight, one could argue that such effects could be the result of a rather unspecific stimulation of all brain tissue located along the route of the current flow from one electrode to the other. This raises the possibility that regional anatomical differences in the conductance may play a crucial role for the distribution of blood flow changes. This is, however, not a likely explanation for the majority of effects found in remote brain regions. First of all, remote effects were located not only in cortical areas, but also in subcortical regions. Secondly, computer-based modelling (Miranda et al., 2006; Wagner et al., 2007) together with the results of studies on the impact of varying the size of the electrodes (e.g., Nitsche et al., 2007) all point clearly to the fact that maximum current density magnitudes are located beneath the electrodes. It can, therefore, be hypothesized that the observed effects in remote brain areas represent modulations of the functional interactions of the stimulated area and the remote areas via cortico-cortical and cortical–subcortical connections (Lang et al., 2005). Whether such transsynaptically mediated effects are behaviourally relevant remains unclear to date. Future neuropharmacological and neuroimaging studies in humans and animals may further characterize the neurophysiological mechanisms underlying rTMS and tDCS by providing indirect evidence about the ion channels and receptors involved in these effects (Liebetanz et al., 2002; Nitsche et al., 2003a, 2004).

Table 2
A selection of studies evaluating the effects of TMS/rTMS on picture naming or related linguistic tasks

	Protocol	Subjects	Region	Task	Main result
Bridgers and Delaney (1989)	sp-TMS; various intensities	30 subjects	Frontocentral bilateral (circular coil)	Oral word association test	Significant performance improvement following stimulation
Claus et al. (1993)	50 Hz rTMS; 500 ms; 100% SO (1T)	44 subjects	L/R temporal–parietal cortex	Verbal comprehension	Left temporal–parietal rTMS increased error rate
Töpper et al. (1998)	sp-TMS; 45–55% SO (1.5T)	65 subjects	WA/R homologue, Broca's area, M1	Picture naming	Left WA stimulation at 0.5 and 1 s before faciltated latency
Flitman et al. (1998)	15 Hz rTMS; 750 ms, 120% MT	7 subjects	L/R inferior frontal region, parietal cortex	Picture-word verification task	Left inferior frontal rTMS impaired performance
Wassermann et al. (1999)	10 Hz rTMS; up to 3 s; 100% MT	14 patients with temporal lobe epilepsy	L/R frontal, mid-superior or posterior temporal	Picture naming/word reading	Naming latencies were reduced following left rTMS independent of stimulation site; no effect on reading
Mottaghy et al. (1999)	20 Hz rTMS; 2 s; 55% SO (2T)	20 subjects	WA/R homologue, Broca's area, V1	Picture naming	20 Hz rTMS to WA decreased latencies up to 2 minutes
Sparing et al. (2001)	20 Hz rTMS; 2 s or 1 Hz; 40 s; 35, 45 or 55% SO (2T)	16 subjects	WA/R homologue, Broca's area, V1	Picture naming	Facilitating effects of rTMS depended on frequency and intensity
Stewart et al. (2001)	10 Hz rTMS; 600 ms; 75% SO (2T)	8 subjects	L/R posterior inferior temporal cortex, vertex	Picture naming	Left temporal rTMS disrupted naming likely due to an effect on object recognition
Knecht et al. (2002)	1 Hz rTMS; 10 min, 110% MT	11 L-, 9 R-hemispheric language dominant subjects	WA/R homologue, vertex	Picture-word verification task	Low frequency rTMS suppressed performance depending on the lateralization of language
Cappa et al. (2002)	20 Hz rTMS, 600 ms, 90% MT	9 subjects	L/R dorsolateral prefrontal cortex	Object-, action naming	Left frontal rTMS shorted naming latency for actions only
Andoh et al. (2006)	1 Hz rTMS; 10 min; 110% MT	12 subjects	Broca's area, WA	Language fragment-detection	Low-frequency rTMS applied over Wernicke's area resulted in decreased reaction times
Naeser et al. (2005)	1 Hz rTMS, 20 min, 90 min, over 10 days	4 chronic poststroke aphasic patients	Right homologue of Broca's area	Picture naming	Significant improvement in naming pictures over 2–8 months
Winhuisen et al. (2005)	4 Hz rTMS; 10 s; 20% SO (2.1T)	11 acute poststroke aphasic patients	L/R inferior frontal gyrus	Picture naming	In some poststroke aphasics, right activation is essential for residual language function

MT, motor threshold; SO, stimulator output; sp, single pulse; T, Tesla; WA, Wernicke's area; L, left; R, right.

Taken together, the data suggest that the degree of variability of the neuromodulatory effects on language processing depends primarily upon the diversity of language tasks used and the stimulation parameters applied. Further differential effects may also result from methodological problems such as the appropriate localization of the targeted brain area due to the inter-individual variations of cortical areas (Sparing et al., in press).

Nevertheless, there seems to exist some consistency across all studies which investigated picture naming or other related language tasks in humans with TMS (for an overview, see Table 2) or direct electrical stimulation through implanted subdural electrodes (e.g., Malow et al., 1996; Sinai et al., 2005): Facilitation is more likely to occur when high-frequency rTMS is applied over PPR, including Wernicke's area. In contrast, picture naming is more vulnerable to low or high-frequency rTMS applied to the inferior frontal cortex, i.e., Broca's area. Consistent with these findings in normal subjects, Naeser et al. (2005) proposed that inhibition of right Broca's homologue might be useful to improve picture naming in chronic aphasic patients. With regard to the hemispheric rivalry hypothesis and current concepts of stroke rehabilitation (for reviews, see, e.g., Hummel and Cohen, 2006; Talelli and Rothwell, 2006), they applied low-frequency (i.e., inhibiting) rTMS to perturbate right Broca's homologue and reported a behavioural benefit in a small number of aphasic patients (Naeser et al., 2005). This concept has, however, been challenged by recent brain imaging studies suggesting that an upregulation with recruitment of homologue language areas in the right hemisphere correlates with language improvement (e.g., Saur et al., 2006; Thiel et al., 2006; Winhuisen et al., 2005). The reasons for these discrepant findings remain unclear. In particular, the contribution of the right hemisphere to the recovery from aphasia remains under debate (for a recent review, see Devlin and Watkins, 2007).

5. Conclusion

Our current results are in good accordance with prior rTMS studies suggesting that naming improvement in aphasics may be achieved by stimulation of the PPR, including Wernicke's area (BA 22). The exact neurophysiological basis of the facilitatory effects of anodal tDCS applied to this brain area remains, however, to be elucidated. At present, tDCS represents a promising tool for non-invasive, non-pharmacological modulation of brain function. The required hardware is easy to handle and inexpensive. The technique has been proven to be safe under the current guidelines and it is, in particular, not associated with the risk of seizure induction inherent to TMS. Nevertheless, more studies are needed to assess the underlying mechanisms and to continually improve the stimulation protocols. If more sustained effects on language performance can be achieved through further technical and methodological refinements, tDCS in combination with logopaedic rehabilitation may help to secure long-term benefits in aphasic patients.

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