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Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation

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Transcranial direct current stimulation is a painless, non-invasive brain stimulation technique that allows one to induce polarity-specific excitability changes in the human brain. Here, we investigated, for the first time in a 'proof of principle' study, the behavioural effect of transcranial direct current stimulation on visuospatial attention in both healthy controls and stroke patients suffering from left visuospatial neglect. We applied anodal, cathoP:dal or sham transcranial direct current stimulation (57 μA/cm^2, 10 min) to the left or right posterior parietal cortex. Using a visual detection task in a group of right-handed healthy individuals (n = 20), we observed that transcranial direct current stimulation enhanced or impaired performance depending on stimulation parameters (i.e. current polarity) and stimulated hemisphere. These results are in good accordance with classic models of reciprocal interhemispheric competition ('rivalry'). In a second experiment, we investigated the potential of transcranial direct current stimulation to ameliorate left visuospatial neglect (n = 10). Interestingly, both the inhibitory effect of cathodal transcranial direct current stimulation applied over the unlesioned posterior parietal cortex and the facilitatory effect of anodal transcranial direct current stimulation applied over the lesioned posterior parietal cortex reduced symptoms of visuospatial neglect. Taken together, our findings suggest that transcranial direct current stimulation applied over the posterior parietal cortex can be used to modulate visuospatial processing and that this effect is exerted by influencing interhemispheric reciprocal networks. These novel findings also suggest that a transcranial direct current stimulation-induced modulation of inter-hemispheric parietal balance may be used clinically to ameliorate visuospatial attention deficits in neglect patients.

Keywords: cortical plasticity; polarization; electrical stimulation; parietal lobe; neglect

Abbreviations: A = anodal; C = cathodal; ER = error rate; P3/P4 = electrode position P3/P4 of the 10/20 EEG system; PPC = posterior parietal cortex; RT = reaction time; (r)TMS = (repetitive) transcranial magnetic stimulation; S = sham; TDCS = transcranial direct current stimulation; TP = time point

Introduction

Unilateral spatial (hemi-)neglect and (hemi-)inattention are clinical terms used to describe a number of different clinical symptoms that have in common the patient's failure to attend to, respond adequately to or orient voluntarily to people or objects on the side of space contralateral to the lesion (Mesulam, 1981). Though visuospatial attention is mediated by a widely distributed network

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of areas in the parietal and frontal cortices of both hemispheres, chronic visuospatial neglect is most reliably observed following lesions in the right hemisphere, and in particular following damage to the posterior parietal cortex (PPC) and the temporo–parietal junction (Vallar and Perani, 1986; Corbetta *et al*., 2000; Halligan *et al*., 2003; Mort *et al*., 2003; Husain and Nachev, 2007). Neglect, unfortunately, limits the degree of active participation in rehabilitation programmes and is thus associated with poor functional recovery and less successful social reintegration (Arene and Hillis, 2007).

Recent studies suggest that non-invasive stimulation techniques, i.e. transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), may become new adjuvant tools to promote recovery of function after stroke (for reviews, see Harris-Love and Cohen, 2006; Hummel and Cohen, 2006; Talelli and Rothwell, 2006; Edwards and Fregni, 2008). For example, the application of TMS has been shown to improve impaired contralesional visuospatial processing in neglect patients (for a review, see Fierro *et al*., 2006). To date, however, the achieved improvements are of transient nature. Unlike TMS, tDCS can be used to polarize neural tissue for a longer period of time (i.e. up to a few hours) through the application of weak direct currents, which are delivered to the cortex via two electrodes placed on the scalp (Nitsche and Paulus, 2000; Paulus, 2003; Wassermann and Grafman, 2005; Fregni and Pascual-Leone, 2007; Sparing and Mottaghy, 2008). If the induced excitability changes outlast the actual stimulation, the term ‘after-effect’ is commonly used. In the motor system, these after-effects depend on polarity, i.e. anodal stimulation ($tDCS_{anodal}$) enhances, while cathodal stimulation ($tDCS_{cathodal}$) decreases cortical excitability up to a few hours (Priori *et al*., 1998; Nitsche and Paulus, 2000, 2001; Nitsche *et al*., 2005, 2008; Wagner *et al*., 2007).

Here, we intended to clarify whether tDCS applied over the PPC can be used to modulate visuospatial attention in (right-handed) healthy individuals and patients with left visuospatial neglect. In the first experiment, healthy subjects performed a visuospatial detection task, which has been proven useful to explore the phenomenon of extinction in TMS studies (Hilgetag *et al*., 2001; Dambeck *et al*., 2006; Meister *et al*., 2006). Error rates and reaction times, measured before and after the application of tDCS, served as outcome measures of task performance. We hypothesized that tDCS can be used to enhance or reduce the ability to detect visual stimuli presented in the left or right visual hemifield depending on the actual stimulation condition (i.e. current polarity: $tDCS_{anodal}$, $tDCS_{cathodal}$ and $tDCS_{sham}$) and side of stimulation (i.e. left or right PPC). Based on the results of the first experiment, we derived stimulation parameters for the second study in which 10 stroke patients suffering from left visuospatial neglect were included. Here, we chose as task the ‘neglect test’ of the ‘Test Battery of Attentional Performance’ (TAP; Zimmermann and Fimm, 1995), a standardized measure of visuospatial attention. In addition, patients were presented with a computerized version of the line bisection task (Fink *et al*., 2000; 2003*b*). Patients with left visuospatial neglect, when asked to bisect a horizontal line, typically bisect the line to the right of the true centre (Heilman and Valenstein, 1979; Schenkenberg *et al*., 1980; Marshall and Halligan, 1989). We expected to observe tDCS to enhance or impair task performance depending on the stimulation side (i.e. lesioned or non-lesioned PPC) and stimulation condition.

Materials and methods

Experiment 1—healthy subjects

Healthy subjects

Twenty healthy subjects (two females, mean age 28.5 ± 5.7 years) without a history of implanted metal objects, seizures or any other neurological or psychiatric disease participated in the experiment. The study was performed in accordance with standard safety guidelines and the declaration of Helsinki. The study was approved by the local ethics committee and all subjects gave written informed consent.

Transcranial direct current stimulation (tDCS)

tDCS stimulation was delivered by a battery-driven, constant current stimulator (neuroConn GmbH, Ilmenau, Germany) using a pair of surface saline-soaked sponge electrodes. A constant current of 1 mA intensity was applied for 10 min complying with current safety guidelines (Nitsche *et al*., 2003*b*; Iyer *et al*., 2005). The first electrode (to which polarity refers, area = 25 cm^2) was placed over P3 or P4 of the international 10–20 system for EEG electrode placement. These locations have previously been shown to overlie PPC in close proximity to the intraparietal sulcus (e.g. Hilgetag *et al*., 2001; Pourtois *et al*., 2001; Sack *et al*., 2002; Herwig *et al*., 2003; Dambeck *et al*., 2006). The reference electrode (area = 35 cm^2) was placed over Cz. The choice of Cz was based on previous studies that investigated the effect of tDCS on primary visual cortex (Antal *et al*., 2004) and parieto–temporal areas (Varga *et al*., 2008). Each hemisphere was tested in a group of 10 subjects.

Three different stimulation sessions were carried out for each hemisphere: (i) $tDCS_{anodal}$ (P3-A/P4-A); (ii) $tDCS_{cathodal}$ (P3-C/P4-C) and for control (iii) sham stimulation, $tDCS_{sham}$ (P3-S/P4-S). $tDCS_{sham}$ was performed in the same way as active stimulation but the stimulator was turned off after 30 s. This ensured that subjects could feel the initial itching sensation at the beginning of tDCS and allowed for a successful blinding of the subjects for the respective stimulation condition (Gandiga *et al*., 2006). The stimulation sessions were separated by at least 1 h with counterbalanced ordering 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 (Vines *et al*., 2006).

Visual detection task

Subjects were seated in a comfortable chair placed in front of a monitor (21″, TFT flat screen, viewing distance 60 cm) in a dimly illuminated room. The screen was aligned to the midsagittal plane of the subject. Stable viewing was supported by a chin-rest. Subjects were instructed to keep fixation at the centre of the screen throughout the experiment. Small black dots of 2×2, 2×3, 3×3, 3×4 or 4×5 pixels were presented at $\sim 23^\circ$ eccentricity left or right of the centre of the screen against a grey background. Eye movements were monitored using an eye-tracker (ViewPoint, Arrington Res. Inc., Scottsdale, AZ, USA), although the large visual eccentricity rendered target saccades unlikely. After an initial block in which all trial sizes were presented, two individual perithreshold sizes were chosen separately for each subject’s hemifield to avoid floor and ceiling effects.

This procedure of stimulus titration was adopted from previous TMS studies (Hilgetag *et al*., 2001; Dambeck *et al*., 2006; Meister *et al*., 2006). Subjects correctly identified 12%–31% (mean: 23%) stimuli of the smaller size and 50%–77% (mean 66%) of the larger stimuli, averaged for left, right and bilateral stimuli. Empty catch trials were presented to prevent subjects from automatically answering regardless of stimulus presentation and to detect those subjects who erroneously reported absent visual stimuli. Subjects used their right hand to report the detection of stimuli: the index finger was used to press the left mouse button for unilateral left visual stimuli, the ring finger was used to press the right mouse button for unilateral right stimuli and the middle finger was used to press the middle mouse button for bilateral stimuli. In the case of catch trials, no button press was required. At the beginning of each trial, a central fixation cross appeared for 1000 ms followed by the stimulus for 40 ms. Subjects had a 2250 ms time window to respond before a new trial began (Supplementary Fig. 1A). The experiment was carried out in blocks of 160 trials each. Each block contained left, right and bilateral stimuli of the previously determined two stimulus sizes, which were presented 20 times each in random order. In addition, 40 catch trials were randomly intermingled within each block (total 160 trials). The total duration of one block of trials was ~7–8 min.

Course of experiment

In each stimulation session ($tDCS_{anodal}$, $tDCS_{cathodal}$ and $tDCS_{sham}$), participants were required to perform three blocks of trials: before tDCS (baseline), immediately after tDCS [timepoint (TP) 1] and 20 min following the cessation of tDCS (TP 2) (Supplementary Fig. 1B). Before each block of trials, there were a few warm-up trials.

Data analysis

The mean error rates (ER) and reaction times (RTs) were calculated for each of the three blocks. Relative percentage scores were computed separately for each of the two blocks performed following tDCS with respect to the baseline measurement, i.e. the block before tDCS using the following equation:

$$RT_{\text{percentage change}} = \left[\frac{RT_{TP1/TP2}}{RT_{baseline}}\right] \times 100.$$

Data were analysed with repeated measure analysis of variance (ANOVA). ANOVA comprised the within-subject factors VISUAL STIMULUS [three levels: contralateral (with respect to tDCS) versus ipsilateral versus bilateral], tDCS [three levels: $tDCS_{anodal}$ versus $tDCS_{cathodal}$ versus $tDCS_{sham}$] and TIME [two levels: TP 1 versus TP 2], as well as HEMISPHERE as the between-subjects factor. Mauchly's test examined sphericity in the ANOVA model. We applied Duncan's 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 14 for Windows software package.

Experiment 2—neglect patients

Patients

In the second experiment, 10 right-handed patients (six females and four males) with left visuospatial neglect due to right-sided cortical and/or subcortical vascular lesions were included. The patient characteristics are detailed in Table 1. The mean age was 57.3 ± 16.9 years. The mean time post-onset of neglect was 2.9 ± 3.5 months. Supplementary Fig. 2 illustrates the lesions of the patients as documented by clinical CT or MRI scans. For inclusion, patients had to show visuospatial neglect symptoms in at least two tasks taken from the 'Test Battery of Attentional Performance' (TAP; Zimmermann and Fimm, 1995) and the 'Neglect Test' (NET; Fels and Geissner, 1996). All patients underwent a standard neurological and neuropsychological assessment including Goldman perimetry and the TAP to exclude visual field deficits. Further exclusion criteria were epilepsy, a history of prior stroke or prior haemorrhage and any severe internal medical disease. Informed consent was given by all patients prior to participation in the study.

Table 1 Patient characteristics

No	Initials	Sex	Age	Aetiology	TPO
1	L.D.	M	80	Vascular: hypertension	2.5
2	H.K.	F	68	Cardioembolic	0.5
3	M.E.	F	28	Cardioembolic	1.3
4	B.S.	F	49	Vascular: diabetes, hypertension, nicotine	12.4
5	K.F.	M	80	Vascular: hypertension, nicotine	1.1
6	S.H.	F	47	ICA dissection	4.2
7	G.M.	M	64	Hypertension	2.9
8	M.R.	M	45	Vascular: hypertension, nicotine	0.8
9	R.H.	F	64	Cardioembolic	1.7
10	R.P.	F	43	ICA dissection	1.2

ICA = internal carotid artery; TPO = time post-onset of neglect (months).

Transcranial direct current stimulation (tDCS)

tDCS was delivered as described above. However, based on the results of Experiment 1, we reduced the number of tDCS conditions to the following four conditions: (i) $tDCS_{anodal}$; (ii) $tDCS_{cathodal}$ stimulation of the contralesional PPC (P3-A and P3-C, respectively); (iii) $tDCS_{anodal}$ and (iv) $tDCS_{sham}$ of the lesioned hemisphere (P4-A and P4-S, respectively). Stimulation sessions were carried out on two separate days with an intersession interval of at least 3 h with the order of stimulation conditions counterbalanced across subjects. The following two tasks were performed before and after the respective tDCS condition.

Tasks

TAP, subtest 'neglect'

In a pilot study ($n = 3$), we had experienced that neglect patients had difficulties to perform the visual detection task of Experiment 1, although difficulty levels were adjusted individually. Therefore, we decided to employ a task frequently used to assess patients, i.e. the 'neglect' subtest of the TAP (Zimmermann and Fimm, 1995). During this task, patients are required to fixate on a central square (size 3.8°) on a black screen. To ensure fixation, patients are asked to read aloud single letters appearing and changing every few seconds at fixation. Around the fixation in each visual hemifield, the display shows 24 randomly distributed white distractors (small, hardly legible two- and three-digit numbers). These stimuli were introduced to enhance left visuospatial neglect via distractors. In the gaps between these distractors, a peripheral three-digit target appeared at random locations in either the left or right visual field within 13° from fixation. These three-digit targets, however, appeared as flickering stimuli. Patients were instructed to press a key with their right index finger as soon as they detected the target. This was presented until the key was pressed or for a maximum of 3 s. In each visual hemifield, 21 targets were presented at different positions. An increase in target detection was investigated by Fisher's exact test considering the number of detected or cancelled stimuli within the left visual hemifield. In addition, RTs were calculated and analysed by ANOVA.

Line bisection task

In a computerized self-paced line bisection task, patients were required to bisect horizontal lines presented on a PC monitor (17″, TFT flatscreen, viewing distance 57 cm). Using a computer mouse to navigate a small red vertical transector, subjects were instructed to mark the centre of the line. A block of trials consisted of 24 trials. Deviations in screen pixels from the true centre were averaged and converted into millimetres. Positive values reflected rightward deviation. ANOVA was performed to assess the overall effect of tDCS conditions on the deviation. Duncan's test was used as the *post hoc* test.

Results

Experiment 1

All subjects tolerated the application of tDCS without any adverse side-effects. Some subjects reported that they felt the electrical current as an itching sensation beneath both electrodes at the onset of tDCS. Their forced guessing concerning the difference between active and sham stimulation was at the chance level. In all experiments, subjects correctly identified catch trials to a high degree (mean correct response 96% ± 7%). Subjects' performance in detecting catch trials following the application of tDCS (correct response rate: $tDCS_{anodal}$, TP1 98% ± 3%, TP2 98% ± 2%; $tDCS_{cathodal}$, TP1 97% ± 5%, TP2 98% ± 3%; $tDCS_{sham}$, TP1 94% ± 12%, TP2 94% ± 11%) was not significantly different from that of the corresponding baseline trials (correct response rate: 96% ± 10%, 96% ± 5% and 97% ± 3%, respectively, $P > 0.16$).

Error rate

Overall, mean percentage changes in the ER ranged between −4.8% and +6.6%. ANOVA with site of VISUAL STIMULUS (three levels), tDCS (three levels) and TIME (two levels) as within-subject factors and HEMISPHERE as the between-subjects factor indicated a significant interaction between VISUAL STIMULUS and tDCS [$F(4,72) = 2.54$; $P < 0.05$] and between VISUAL STIMULUS, tDCS and TIME [$F(4,72) = 2.70$; $P < 0.04$]. The calculations of *post hoc* contrasts using Duncan's test revealed that $tDCS_{anodal}$ compared to sham tDCS increased subjects' accuracy in detecting visual stimuli presented in the contralateral (i.e. with respect to the tDCS stimulation site) hemifield (106.5% ± 9.7%; $P < 0.01$) (Fig. 1A). In contrast, $tDCS_{cathodal}$ compared to sham tDCS impaired the detection of contralateral stimuli (95.2% ± 5.7%; $P < 0.03$). The detection of visual stimuli in the subject's ipsilateral hemifield was unaffected despite a trend towards a better performance following $tDCS_{cathodal}$ (103.4% ± 10.0%; $P = 0.08$). However, a direct comparison between $tDCS_{cathodal}$ and $tDCS_{anodal}$ revealed that current polarity altered the performance reversely ($P < 0.05$).

Recognition of bilateral visual stimuli deteriorated following $tDCS_{cathodal}$ only (94.9% ± 10.1%; $P < 0.03$). A more detailed analysis of incorrect responses for bilateral visual stimuli showed a significantly increased number of reported ipsilateral visual stimuli, when $tDCS_{cathodal}$ was delivered over left or right PPC, respectively ($P < 0.05$). This indicates that the contralateral stimulus of a simultaneously presented bilateral stimulus pair went undetected (i.e. suggesting contralateral extinction). The effect of $tDCS_{anodal}$ on bilateral visual stimuli did not differ from $tDCS_{sham}$ ($P > 0.9$), meaning that no significant changes in performance were seen for unilateral as well as bilaterally presented visual stimuli following $tDCS_{anodal}$. *Post hoc* analysis of the data acquired 20 min following the cessation of tDCS revealed that there were no longer any significant differences between single factors ($P > 0.3$) (Fig. 1B). The observed trends were nearly mirror symmetrical for stimulation of the right and left PPC, indicating

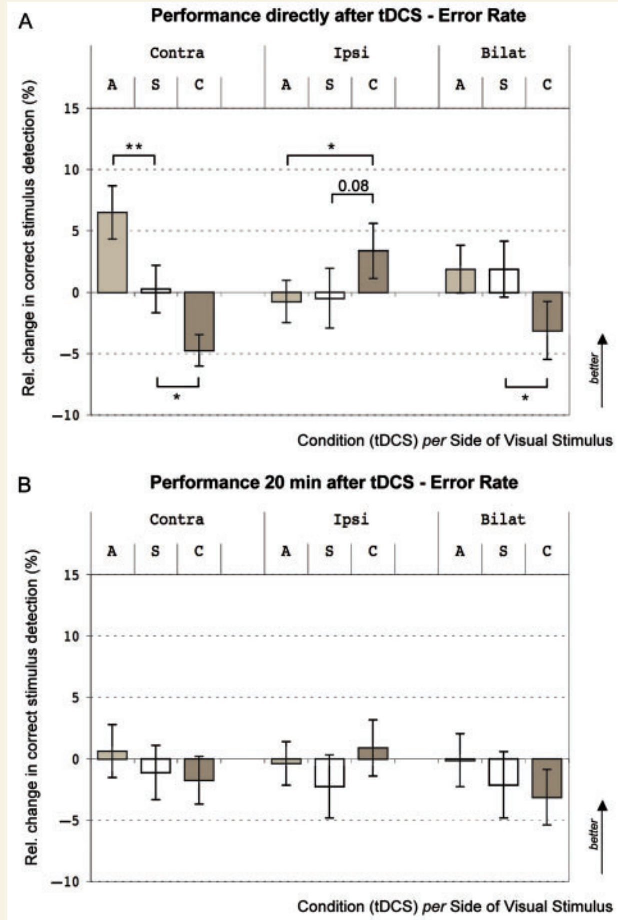

Figure 1 Error rates in the visuospatial detection task (Experiment 1, healthy subjects) directly after (**A**) and 20 min after (**B**) the application of tDCS to the posterior parietal cortex. A significant interaction between tDCS condition (A = $tDCS_{anodal}$; S = $tDCS_{sham}$; C = $tDCS_{cathodal}$) and visual stimulus location (Contra = visual stimulus was presented in the contralateral hemifield with respect to tDCS, Ipsi = visual stimulus was ipsilaterally presented, Bilat = visual stimuli were presented bilaterally and simultaneously) was found ($P < 0.05$). In particular, real tDCS significantly influenced the visual stimulus detection in the contralateral hemifield. The modulatory effect resolved after 20 min (**B**). Bars indicate standard errors (SE). $^{**}P < 0.01$, $^{*}P < 0.05$.

that both brain areas made similar contributions to the control of visuospatial attention. Thus, no significant effect of site of stimulation (HEMISPHERE) was observed ($P = 0.62$).

Reaction times

For RTs, ANOVA with site of VISUAL STIMULUS (three levels), tDCS (three levels) and TIME (two levels) as within-subject factors and HEMISPHERE as the between-subjects factor demonstrated no significant main effect or interaction (Supplementary Fig. 3A). To assess whether tDCS affected performance *per se* (i.e. with respect to their corresponding baseline condition), we additionally carried out Wilcoxon signed-rank tests, in which each condition was tested against 100% (i.e. 100% representing no RT change). The percentage change in the mean RTs for detection of visual stimuli in the contralateral hemifield following $tDCS_{anodal}$ (94.9% ± 7.6%) was significantly different from 100% ($P < 0.01$), indicating that $tDCS_{anodal}$ speeded response times. $tDCS_{anodal}$ decreased response times also for visual stimuli presented ipsilaterally (95.5% ± 8.6%, $P < 0.01$). Moreover, the facilitation of RTs was still present after 20 min for contralateral stimuli in comparison with the observed effect on the ER (94.3% ± 8.9%, $P < 0.01$) (Supplementary Fig. 3B).

Experiment 2

TAP, subtest 'neglect'

The number of detected or cancelled stimuli within the left visual hemifield (Fisher's exact test) did not improve in any of the four conditions. Following the analysis of mean RTs, patients tended to respond faster to stimuli presented in the left visual hemifield following 'real' tDCS when compared to sham stimulation (Fig. 2A). The largest facilitation was observed after $tDCS_{anodal}$ of the lesioned hemisphere (P4-A: −61 ms ± 55ms). The interindividual variance was, however, high. ANOVA with the factors time (two levels) and condition (four levels) did not reveal any significant main effect or interaction. $tDCS_{anodal}$ applied to the unlesioned hemisphere tended to increase the number of detected stimuli (P3-C: 0.6 ± 0.4). ANOVA with ER as the dependent factor did not show any statistically significant effects either (Fig. 2B).

Line bisection task

Deviations from the centre of the line for all four experimental conditions are summarized in Fig. 3. As expected, patients showed under all four baseline conditions a rightward deviation reflecting left visuospatial neglect (mean deviation 4.3 ± 1.2 mm). ANOVA with time (two levels) and condition (four levels) as within-subject factors showed a significant main effect of time [$F(1, 9) = 6.01$, $P = 0.04$]. The calculation of *post hoc* contrasts revealed that both $tDCS_{anodal}$ of the lesioned hemisphere (P4-A) and $tDCS_{cathodal}$ of the unlesioned hemisphere (P3-C) caused a significant reduction in the rightward bias, even leading to a small leftward bias under both conditions (P4A: pre-tDCS 3.4 mm, post-tDCS −1.5, $P < 0.05$; P3C: pre-tDCS 5.4, post-tDCS −1.7, $P < 0.01$). No significant effect on deviation was observed following $tDCS_{anodal}$ of the unlesioned hemisphere (P3-A) or $tDCS_{sham}$ (P4-S).

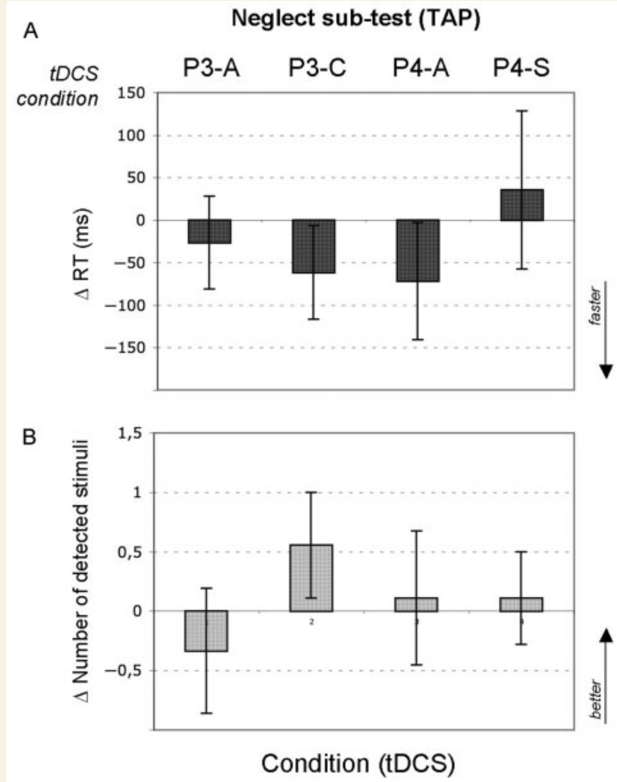

Figure 2 Results of the subtest 'neglect' of the TAP. No significant changes in performance were detected, with only a tendency of cathodal stimulation above the unlesioned posterior parietal cortex towards enhancing performance in the neglect patients. P3/4 refers to the international 10–20 EEG system. A = $tDCS_{anodal}$, S = $tDCS_{sham}$; C = $tDCS_{cathodal}$.

Figure 4 illustrates the spatial shifts induced by $tDCS_{anodal}$ of the lesioned hemisphere (P4-A) or $tDCS_{cathodal}$ of the unlesioned hemisphere (P3-C) in each individual subject, respectively. Despite the heterogeneity of the patients, improvement was consistently found following $DCS_{cathodal}$ of the unlesioned hemisphere (P3-C). The magnitude of improvement (i.e. reduction of rightward bias) and the estimated lesion size (cm^2) were correlated using Spearman's rank correlation tests. The results (P3-C: $R = -0.66$, $P = 0.04$; P4-A: $R = -0.43$, $P = 0.2$) suggest that lesion size negatively correlated with the magnitude of improvement, in particular following $tDCS_{cathodal}$ to the unlesioned hemisphere. This result needs therefore to be confirmed in larger trials systematically investigating the relationship between the neuromodulatory effect and lesion size and location, respectively.

Discussion

This is the first study to show a modulation of visuospatial processes by means of tDCS applied over the posterior parietal lobe in humans. In healthy subjects, stimulation bidirectionally modulated visuospatial task performance depending on both side of stimulation and current polarity: $tDCS_{anodal}$ applied over the

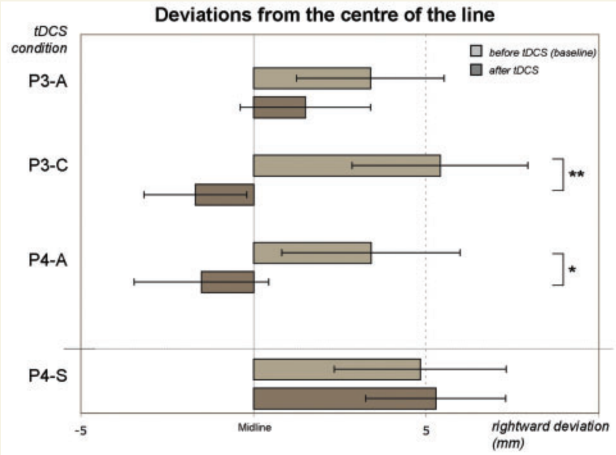

Figure 3 Results of the computerized line bisection task. In all four baseline conditions (bars in light grey), neglect patients showed a rightward deviation reflecting left hemispatial neglect. Both, $tDCS_{anodal}$ of the lesioned hemisphere (P4-A) and $tDCS_{cathodal}$ of the unlesioned hemisphere (P3-C) caused a significant reduction in the rightward bias, even leading to a small leftward bias in both cases. No significant modulatory effect on deviation was observed following $tDCS_{anodal}$ of the unlesioned hemisphere (P3-A) or $tDCS_{sham}$ (P4-S). P3/4 refers to the international 10–20 EEG system. A = $tDCS_{anodal}$; S = $tDCS_{sham}$; C = $tDCS_{cathodal}$. $^{**}P<0.01$, $^{*}P<0.05$.

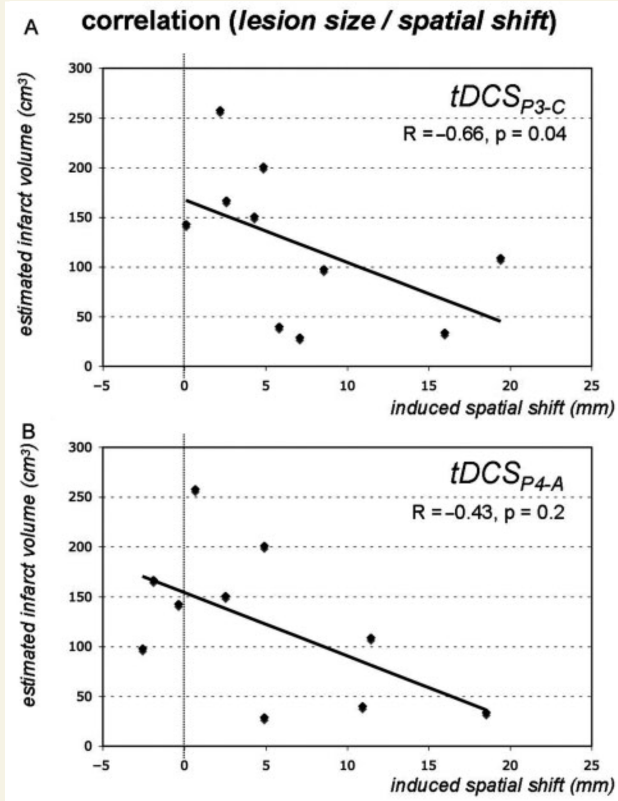

Figure 4 Individual results of the computerized line bisection task ($n = 10$) with respect to the estimated lesion size (cm^3). The details of the lesion mapping procedure have been described elsewhere (Weiss *et al*., 2008). The *x*-axis refers to the spatial shift following $tDCS_{anodal}$ of the lesioned hemisphere (**A**, P4-A) and $tDCS_{cathodal}$ of the unlesioned hemisphere (**B**, P3-C), respectively. Positive values reflect a bias towards the left and vice versa (mm). Despite the heterogeneity of the patients, improvement was consistently found following $DCS_{cathodal}$ of the unlesioned hemisphere (P3-C). The correlation analysis suggests that lesion size negatively correlated with the magnitude of improvement, in particular following $tDCS_{cathodal}$ to the unlesioned hemisphere.

right or left PPC biased visuospatial attention towards the contralateral hemispace. The opposite effect was observed when the electrical current flowed in the reverse direction, i.e. after $tDCS_{cathodal}$. These findings are in good accordance with previous studies using 'inhibitory' (i.e. low-frequency) or 'facilitatory' (i.e. high-frequency) rTMS to influence PPC function in humans (e.g. Fierro *et al*., 2000, Hilgetag, *et al*., 2001; Kim *et al*., 2005, Thut *et al*., 2005; Babiloni *et al*., 2007; Nyffeler *et al*., 2008) and cathodal tDCS in cats (Schweid et al, 2008). These findings are also consistent with our previous work where we used galvanic vestibular stimulation to modulate the egocentric reference frame (Fink *et al*., 2003).

At first sight, it may seem contradictory that not only facilitation but also inhibition of intact brain areas may result in enhanced task performance. However, such 'paradoxical' facilitation is known as the 'Sprague effect' from animal studies (Sprague, 1966) and has also been reported in patients (Kapur, 1996; Vuilleumier *et al*., 1996). Furthermore, our results are fully consistent with the classic concept of hemispheric rivalry originally proposed by Kinsbourne (1977). This model provides an explanation for the phenomenon of extinction suggesting that both parietal lobes may exert reciprocal interhemispheric inhibition. Hence, simultaneous presentation of a competing stimulus activating the intact hemisphere may lead to a further suppression of the lesioned hemisphere thereby reducing the 'perceptual weight' of the contralesional stimulus, consistent with functional imaging data showing that such competition may impact even at earlier levels of visual processing (Fink *et al*., 2000*a*). Further support for the rivalry hypothesis stems from animal studies, which used a method of reversible cooling for the deactivation of focal brain areas in cats: first, unilateral deactivation of the PPC results in contralateral visuospatial neglect that could be reversed by subsequent deactivation of the same region in the opposite hemisphere (Lynch and McLaren, 1989; Lomber and Payne, 1996; Lomber *et al*., 2002; Payne *et al*., 2003). More recently, we have been able to employ rTMS applied over the contralesional M1 to improve impaired hand function in subcortical stroke patients (Dafotakis *et al*., 2008; Grefkes *et al*. 2008).

Likewise, tDCS seems to be capable of inducing a disturbance of the interparietal balance, in the case of $tDCS_{anodal}$ in favour of the stimulated hemisphere, and in the case of $tDCS_{cathodal}$ in favour of the non-stimulated hemisphere. The resulting attentional bias would account, at least in part, for the opposite effects on perception in the contra- and ipsilateral hemispaces according to Kinsbourne's theory of interhemispheric competition through transcallosal inhibition.

Results in neglect patients

We observed that both $tDCS_{anodal}$ (i.e. 'facilitating' tDCS) of the lesioned PPC and $tDCS_{cathodal}$ (i.e. 'inhibiting' tDCS) of the unlesioned PPC ameliorated the visuospatial deficit in our group of neglect patients as shown by a reduction of the rightward bias in the line bisection task. This pattern of results is consistent with the findings in our group of healthy subjects. Due to the heterogeneity of neglect patients, this part of our study needs to be replicated in a larger patient sample. Our findings are, however, supported by reports that both the upregulation of excitability of the lesioned motor cortex and the downregulation of the homologue area in the intact hemisphere can result in improvement of motor function in stroke patients suffering from motor deficits (for reviews, see Hummel and Cohen, 2006; Edwards and Fregni, 2008). Furthermore, Oliveri *et al*. (2001) used rTMS of the unaffected hemisphere to transiently reduce contralesional visuospatial neglect, a finding which was also replicated by Brighina and co-workers (2003). One may argue that the inhibition of the unlesioned left hemisphere results in an additional 'rightward' neglect, thus adding a leftward bias rather than decreasing the pathological rightward bias. We cannot exclude this possibility from our data with the effect found only in the bisection task. Previous work including animal studies (Lynch and McLaren, 1989; Sprague, 1996; Lomber *et al*., 2002), lesions studies (Vuilleumier *et al*., 1996) and TMS studies in patients (Oliveri *et al*., 2001; Brighina *et al*., 2003) and healthy individuals (Dambeck *et al*., 2006) does not, however, support this notion.

In comparison with the healthy individuals, the tDCS-induced behavioural effect was much more variable in the patient group. Such effects are well known to those who study patient's samples. Furthermore, that we were able to detect significant behavioural changes in the line bisection task, but not in the TAP task, is also likely to reflect the interindividual diversity of neuropsychological deficits within the clinical syndrome of visuospatial (hemi-)neglect (Marshall and Halligan, 1995). Furthermore, while line bisection has been repeatedly shown to draw upon PPC along the intraparietal sulcus (Fink *et al*., 2000, 2001, 2003*b*), extinction has been associated with lesions of the temporo–parietal junction and deep cortico–subcortical damage of the paraventricular occipital white matter (Vallar *et al*., 1994; Halligan *et al*., 2003; Karnath *et al*., 2003; Meister *et al*., 2006). Therefore, the site of stimulation may interfere with the modulation of task performance.

General remarks

In recent years, most progress in the development of novel rehabilitative treatment strategies, which use non-invasive brain stimulation techniques to modulate cortical excitability, has been made in the recovery of motor function. In stroke patients, it has been shown that improvement in motor function can be achieved either by the upregulation of excitability of the lesioned motor cortex or the downregulation of the homologue area in the intact hemisphere (Hummel and Cohen, 2006; Talelli and Rothwell, 2006; Edwards and Fregni 2008). Using fMRI and rTMS, we recently studied changes of cortical connectivity between the two motor networks of the lesioned and non-lesioned hemisphere (Grefkes *et al*., 2008). As expected, rTMS could be used to normalize interhemispheric inhibition and thereby improve impaired hand function (Nowak *et al*., 2008). Nevertheless, it still remains an open question whether interhemispheric competition represents a principle that can be generalized to other brain functions. For instance, Naeser and coworkers (2005) proposed that a downregulation of Broca's homologue in the right hemisphere by means of rTMS may facilitate language recovery in aphasics. This view has, however, been challenged by other TMS and neuroimaging studies suggesting a more complex multilevel process of language recovery in aphasics (Winhuisen *et al*., 2005; Saur *et al*., 2006). Thus, we still need to clarify whether and, if so, at which stages the contralesional hemisphere contributes to the recovery of function or whether its involvement may represent a maladaptive process potentially interfering with the rehabilitative process. In any case, there is considerable evidence for the existence of hemispheric rivalry between the parietal cortices, which play a key role in visuospatial attention and stroke-induced deficits thereof (Vallar and Perani, 1986; Corbetta *et al*., 2000; Halligan *et al*., 2003; Mort *et al*., 2003). Using TMS, transient modulation of the interhemispheric balance has been demonstrated in healthy subjects and visuospatial tasks (e.g. single pulse TMS: Nager *et al*., 2004; Dambeck *et al*., 2006; Meister *et al*., 2006; repetitive TMS: Pascual-Leone *et al*., 1994; Fierro *et al*., 2000; Hilgetag *et al*., 2001; Bjoertomt *et al*., 2002; Kim *et al*., 2005; Thut *et al*., 2005; Babiloni *et al*., 2007; Nyffeler *et al*., 2008) and patients (Oliveri *et al*., 2001; Brighina *et al*. 2003; Fierro *et al*., 2006; Shindo *et al*., 2006). In patients with neglect caused by stroke, rTMS of the unaffected hemisphere transiently improved contralesional neglect and extinction. The present data extend these previous results by showing that tDCS applied over PPC can be used to ameliorate neglect symptoms. In contrast to previous TMS/rTMS studies, which did not directly compare 'inhibitory' and 'facilitatory' stimulation protocols, we observed a clear interaction between stimulation side and type of stimulation (i.e. inhibitory or facilitatory). To the best of our knowledge, we demonstrate for the first time an enhancement in performance resulting from a 'facilitatory' stimulation of the lesioned cortex in neglect patients. Similar observations have recently been made in hemiparetic stroke patients following both anodal tDCS and rTMS (and Theta Burst Stimulation, i.e. a distinct 'facilitatory' rTMS protocol, respectively), applied to the lesioned motor cortex (Hummel *et al*., 2005; Kim *et al*., 2006; Talelli *et al*., 2007). Furthermore, $tDCS_{anodal}$ shortened RTs irrespective of contralateral or ipsilateral presentation of visual stimuli. This behavioural effect that lasted longer in comparison with the changes in ER may result from an effect of $tDCS_{anodal}$ on parietal networks involved in the control of intrinsic alertness (e.g. Sturm *et al*., 1999; Thimm *et al*., 2006). Consistent with this suggestion, recent imaging and lesion studies have revealed non-spatial functions of the inferior parietal regions, such as sustaining attention and controlling attention over time (Husain and Nachev, 2007). Further investigations may disentangle the influence of tDCS on different parietal networks, in particular on those engaged in spatial attention, spatial orientation and intrinsic alertness.

It should be noted that TMS and tDCS act upon neurons differentially (for a review, see Wagner *et al*., 2007). Whereas TMS is thought to lead directly to neuronal excitation, it has been hypothesized that tDCS modulates the resting membrane potentials of neurons and their spontaneous firing rate. Early animal studies have shown that weak cathodal stimulation decreases cerebral excitability due to membrane hyperpolarization, while anodal stimulation increases it by membrane depolarization (Bindman *et al*., 1962; Purpura and McMurtry, 1965; Nitsche and Paulus, 2000). Recent pharmacological studies furthermore suggest that the effects of rTMS and tDCS are mediated through different intracortical neuronal receptors particularly depending on the stimulation protocol, e.g. on stimulation frequency (rTMS) and current polarity (tDCS) (tDCS: Liebetanz *et al*., 2002; Nitsche *et al*., 2003a, 2004, 2006; TMS: Ziemann, 2004; Ziemann *et al*., 2006). Using computer-based modelling, it has been argued that the injected electric current densities by tDCS are smaller in magnitude (A/cm^2) but locally more widely spread than the current densities resulting from TMS (Miranda *et al*., 2006; Silva *et al*., 2008). The current densities are estimated to be maximal beneath the stimulation electrode and to decrease very rapidly with distance from it (Rush and Driscoll, 1968; Miranda *et al*., 2006; Wagner *et al*., 2007). Depending on the strength of the current, electrode size and position the cortical current density magnitudes are far lower than action potential thresholds from controlled electrical stimulation experiments (by factor 10–100) (Wagner *et al*., 2007). Nevertheless tDCS magnitudes have been shown to be capable of influencing cortical neurons (e.g. their spontaneous activity) suggesting that the mechanisms of action of tDCS may be quite different from that of TMS and direct cortical stimulation (Wagner *et al*., 2007; Nitsche *et al*., 2008).

Non-invasive neuromodulation by means of tDCS proved to be safe under the current guidelines (Nitsche *et al*., 2003b, 2008; Iyer *et al*., 2005). Most notably, it seems not to be associated with the risk of seizure induction inherent to TMS. Although tDCS has the drawback of a relatively low spatial and temporal resolution, it provides definite advantages such as low costs, easy handling, lack of significant side-effects and a potentially higher magnitude and longer-lasting nature of its modulatory effects in comparison with magnetic stimulation.

Conclusion

In recent years, tDCS effects on performance in non-motor tasks have been increasingly reported, e.g. in sensory processing (Ragert *et al*., 2008), memory (e.g. Fregni *et al*., 2005; Vines *et al*., 2006), learning (e.g. Kincses *et al*., 2004), executive functions (e.g. Fecteau *et al*., 2007; Priori *et al*., 2008), language (e.g. Iyer *et al*., 2005; Sparing *et al*., 2008) or visual perception (e.g. Antal *et al*., 2004). Our current results provide novel evidence that tDCS applied over PPC can be used to bidirectionally modulate visuospatial task performance in healthy individuals as well as neglect patients in accordance with the concept of hemispheric rivalry. In order to advance the therapeutic application of tDCS in the rehabilitation of neglect patients, it still remains an important issue to achieve robust and lasting behavioural effects. Studies in stroke patients with motor deficits suggest that the repetitive application of tDCS in multiple sessions can be used to potentiate the neuromodulatory effects and may thus open up new neurorehabilitative avenues (Khedr *et al*., 2005). Further studies need to clarify which additional factors (e.g. time elapsed since symptome onset, lesion location/size) influence the individual response to tDCS. Further technical and methodological refinements (e.g. optimization of stimulation protocols and electrode positioning) and/or investigations of combinations of tDCS with rTMS and/or other rehabilitative treatment strategies such as sensory stimulation (e.g. caloric, optokinetic, vestibular, transcutaneous electrical; for a review, see Kerkhoff, 2003) may also help to sculpt adaptive brain processes after a stroke in such a way that sustained success is achieved in the amelioration of neglect symptoms.

Supplementary material

Supplementary material is available at *Brain* online.

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