

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, cathodal or sham transcranial direct current stimulation (57 μ A/cm², 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 interhemispheric 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 (Pascual-Leone *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; 2003b). 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.*, 2003b; Iyer *et al.*, 2005). The first electrode (to which polarity refers, area = 25 cm²) 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 cm²) 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 ~23° 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:

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

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

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).

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.

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 $96\% \pm 7\%$). Subjects' performance in detecting catch trials following the application of tDCS (correct response rate: tDCS_{anodal}, TP1 $98\% \pm 3\%$, TP2 $98\% \pm 2\%$; tDCS_{cathodal}, TP1 $97\% \pm 5\%$, TP2 $98\% \pm 3\%$; tDCS_{sham}, TP1 $94\% \pm 12\%$, TP2 $94\% \pm 11\%$) was not significantly different from that of the corresponding baseline trials (correct response rate: $96\% \pm 10\%$, $96\% \pm 5\%$ and $97\% \pm 3\%$, 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 ($106.5\% \pm 9.7\%$; $P < 0.01$) (Fig. 1A). In contrast, tDCS_{cathodal} compared to sham tDCS impaired the detection of contralateral stimuli ($95.2\% \pm 5.7\%$; $P < 0.03$). The detection of visual stimuli in the subject's ipsilateral hemifield was unaffected despite a trend towards a better performance following tDCS_{cathodal} ($103.4\% \pm 10.0\%$; $P = 0.08$). 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 ($94.9\% \pm 10.1\%$; $P < 0.03$). A more detailed analysis of incorrect responses for bilateral visual stimuli showed a

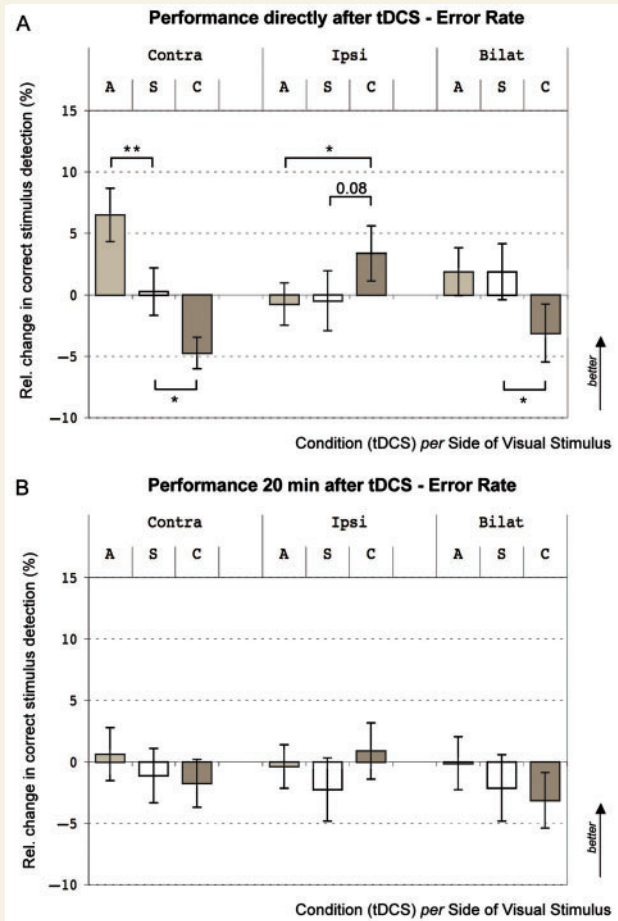


Figure 1 Error rates in the visuospatial detection task (Experiment 1, healthy subjects) directly after (A) and 20 min after (B) the application of tDCS to the posterior parietal cortex. A significant interaction between tDCS condition (A = tDCS_{anodal}; S = tDCS_{sham}; C = tDCS_{cathodal}) and visual 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). ** $P < 0.01$, * $P < 0.05$.

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

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} ($94.9\% \pm 7.6\%$) 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 ($95.5\% \pm 8.6\%$, $P<0.01$). Moreover, the facilitation of RTs was still present after 20 min for contralateral stimuli in comparison with the observed effect on the ER ($94.3\% \pm 8.9\%$, $P<0.01$) (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: $-61\text{ ms} \pm 55\text{ms}$). 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 $4.3 \pm 1.2\text{ mm}$). 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).

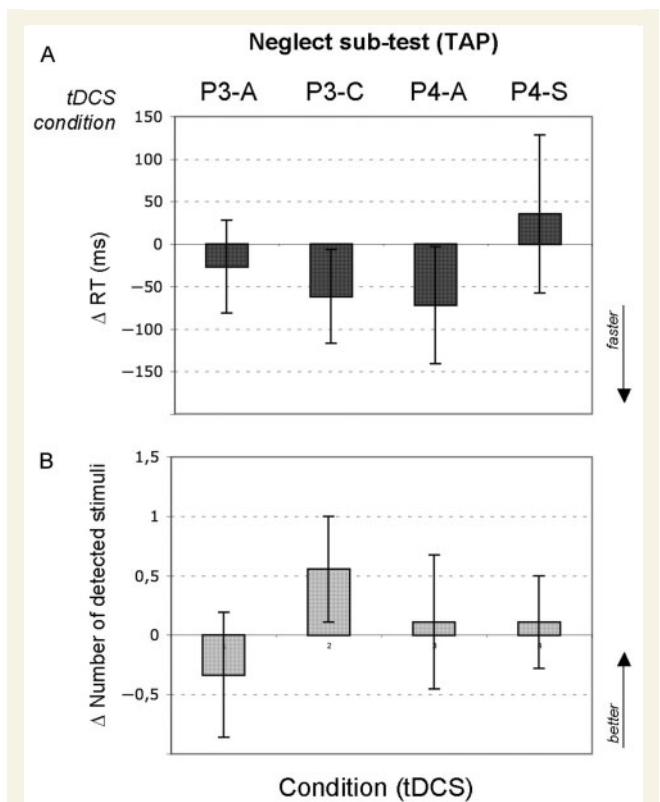
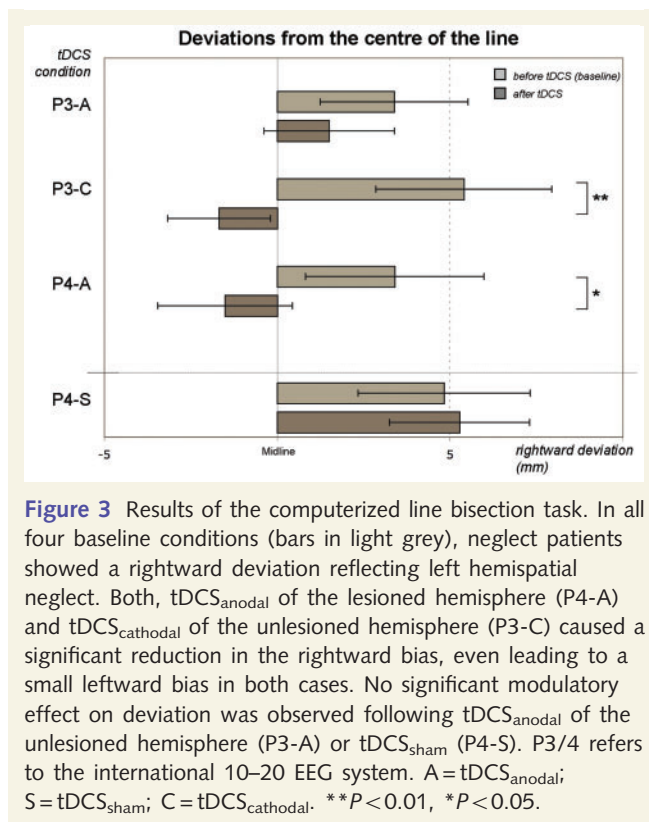


Figure 2 Results of the subtest 'neglect' of the TAP. No significant changes in performance were detected, with only a tendency of cathodal stimulation above the unlesioned posterior parietal cortex towards enhancing performance in the neglect patients. P3/4 refers to the international 10–20 EEG system. 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 neuro-modulatory effect and lesion size and location, respectively.

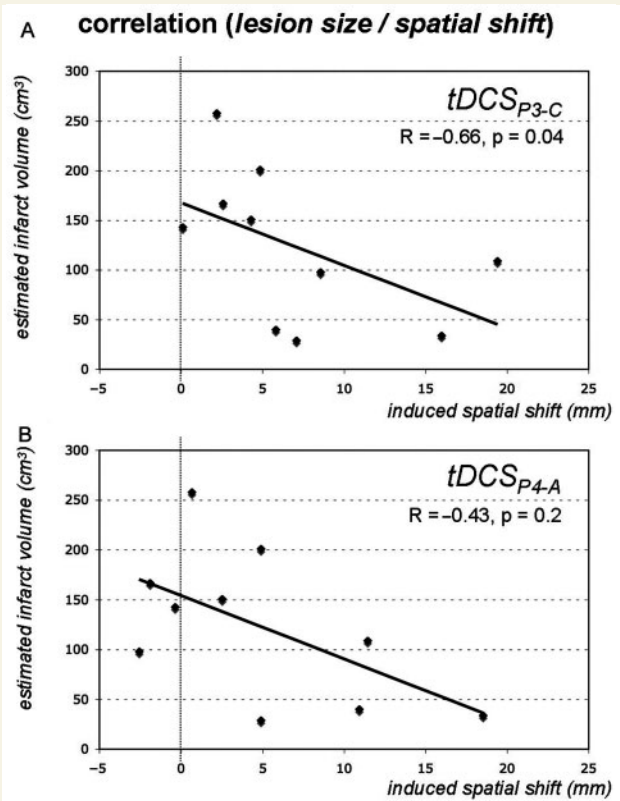
Discussion

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



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.*, 2000a). 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, 2003b), 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 symptom 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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References

- Antal A, Kincses TZ, Nitsche MA, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. *Invest Ophthalmol Vis Sci* 2004; 45: 702–7.
- Arene NU, Hillis AE. Rehabilitation of unilateral spatial neglect and neuroimaging. *Eura Medicophys* 2007; 43: 255–69.
- Babiloni C, Vecchio F, Rossi S, De Capua A, Bartalini S, Olivelli M, et al. Human ventral parietal cortex plays a functional role on visuospatial attention and primary consciousness. A repetitive transcranial magnetic stimulation study. *Cereb Cortex* 2007; 17: 1486–92.
- Bindman LJ, Lippold OC, Redfearn JW. Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. *Nature* 1962; 196: 584–5.
- Bjoertomt O, Cowey A, Walsh V. Spatial neglect in near and far space investigated by repetitive transcranial magnetic stimulation. *Brain* 2002; 125: 2012–22.
- Brighina F, Bisiach E, Oliveri M, Piazza A, La Bua V, Daniele O, et al. 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. *Neurosci Lett* 2003; 336: 131–3.
- Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nat Neurosci* 2000; 3: 292–7.

- Dafotakis M, Grefkes C, Eickhoff SB, Karbe H, Fink GR, Nowak DA. Effects of rTMS on grip force control following subcortical stroke. *Exp Neurol* 2008; 211: 407–12.
- Dambeck N, Sparing R, Meister IG, Wienemann M, Weidemann J, Topper R, et al. Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Res* 2006; 1072: 194–9.
- Edwards D, Fregni F. Modulating the healthy and affected motor cortex with repetitive transcranial magnetic stimulation in stroke: development of new strategies for neurorehabilitation. *NeuroRehabilitation* 2008; 23: 3–14.
- Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *J Neurosci* 2007; 27: 12500–5.
- Fels M, Geissner E. Neglect-Test (NET). Göttingen. Germany: Hogrefe; 1996.
- Fierro B, Brighina F, Bisiach E. Improving neglect by TMS. *Behav Neurol* 2006; 17: 169–76.
- Fierro B, Brighina F, Oliveri M, Piazza A, La Bua V, Buffa D, et al. Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *Neuroreport* 2000; 11: 1519–21.
- Fink GR, Driver J, Rorden C, Baldeweg T, Dolan RJ. Neural consequences of competing stimuli in both visual hemifields: a physiological basis for visual extinction. *Ann Neurol* 2000a; 47: 440–6.
- Fink GR, Marshall JC, Weiss PH, Stephan T, Grefkes C, Shah NJ, et al. Performing allocentric visuospatial judgments with induced distortion of the egocentric reference frame: an fMRI study with clinical implications. *Neuroimage* 2003; 20: 1505–17.
- Fink GR, Marshall JC, Shah NJ, Weiss PH, Halligan PW, Grosse-Ruyken M, et al. Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fMRI. *Neurology* 2000b; 54: 1324–31.
- Fink GR, Marshall JC, Weiss PH, Zilles K. The neural basis of vertical and horizontal line bisection judgments: an fMRI study of normal volunteers. *Neuroimage* 2001; 14: 559–67.
- Fregni F, Boggio PS, Nitsche M, Bormpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Exp Brain Res* 2005; 166: 23–30.
- Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology perspectives on the therapeutic potential of rTMS and tDCS. *Nat Clin Pract Neurol* 2007; 3: 383–93.
- Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol* 2006; 117: 845–50.
- Grefkes C, Nowak DA, Eickhoff SB, Dafotakis M, Küst J, Karbe H, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann Neurol* 2008; 63: 236–46.
- Halligan PW, Fink GR, Marshall JC, Vallar G. Spatial cognition: evidence from visual neglect. *Trends Cogn Sci* 2003; 7: 125–133.
- Harris-Love ML, Cohen LG. Noninvasive cortical stimulation in neurorehabilitation: a review. *Arch Phys Med Rehabil* 2006; 87: S84–93.
- Heilman KM, Valenstein E. Mechanisms underlying hemispatial neglect. *Ann Neurol* 1979; 5: 166–70.
- Herwig U, Satrapi P, Schönfeldt-Lecuona C. Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topogr* 2003 Winter; 16: 95–9.
- Hilgetag CC, Théoret H, Pascual-Leone A. Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nat Neurosci* 2001; 4: 953–7.
- Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain* 2005; 128: 490–9.
- Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol* 2006; 5: 708–12.
- Husain M, Nachev P. Space and the parietal cortex. *Trends Cogn Sci* 2007; 11: 30–6.
- Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology* 2005; 64: 872–5.
- Kapur N. Paradoxical functional facilitation in brain-behaviour research. A critical review. *Brain* 1996; 119: 1775–90.
- Karnath HO, Himmelbach M, Küker W. The cortical substrate of visual extinction. *Neuroreport* 2003; 14: 437–42.
- Kerkhoff G. Modulation and rehabilitation of spatial neglect by sensory stimulation. *Prog Brain Res* 2003; 142: 257–71.
- Kim YH, Min SJ, Ko MH, Park JW, Jang SH, Lee PK. Facilitating visuospatial attention for the contralateral hemifield by repetitive TMS on the posterior parietal cortex. *Neurosci Lett* 2005; 382: 280–5.
- Kim YH, You SH, Ko MH, Park JW, Lee KH, Jang SH, et al. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke* 2006; 37: 1471–6.
- Kincses TZ, Antal A, Nitsche MA, Bártfai O, Paulus W. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. *Neuropsychologia* 2004; 42: 113–7.
- Kinsbourne M. Hemi-neglect and hemisphere rivalry. *Adv Neurol* 1977; 18: 41–9.
- Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology* 2005; 65: 466–8.
- Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain* 2002; 125: 2238–47.
- Lomber SG, Payne BR. Removal of two halves restores the whole: reversal of visual hemineglect during bilateral cortical or collicular inactivation in the cat. *Vis Neurosci* 1996; 13: 1143–56.
- Lomber SG, Payne BR, Hilgetag CC, Rushmore J. Restoration of visual orienting into a cortically blind hemifield by reversible deactivation of posterior parietal cortex or the superior colliculus. *Exp Brain Res* 2002; 142: 463–74.
- Lynch JC, McLaren JW. Deficits of visual attention and saccadic eye movements after lesions of parietooccipital cortex in monkeys. *J Neurophysiol* 1989; 61: 74–90.
- Marshall JC, Halligan PW. When right goes left: an investigation of line bisection in a case of visual neglect. *Cortex* 1989; 25: 503–15.
- Marshall JC, Halligan PW. Within- and between-task dissociations in visuo-spatial neglect: a case study. *Cortex* 1995; 31: 367–76.
- Meister IG, Wienemann M, Buelte D, Grünwald C, Sparing R, Dambeck N, et al. Hemineglect induced by transcranial magnetic stimulation over the right temporo-parietal junction. *Neuroscience* 2006; 142: 119–23.
- Mesulam MM. A cortical network for directed attention and unilateral neglect. *Ann Neurol* 1981; 10: 309–25.
- Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. *Clin Neurophysiol* 2006; 117: 1623–9.
- Mort DJ, Malhotra P, Mannan SK, Rorden C, Pambakian A, Kennard C, et al. The anatomy of visual neglect. *Brain* 2003; 126: 1986–97.
- Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M, et al. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. *Brain Lang* 2005; 93: 95–105.
- Nager W, Wolters C, Münte TF, Johannes S. Transcranial magnetic stimulation to the parietal lobes reduces detection of contralateral somatosensory stimuli. *Acta Neurol Scand* 2004; 109: 146–50.
- Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation* 2008; 1: 206–23.
- Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced

- by transcranial direct current stimulation in humans. *J Physiol* 2003a; 553: 293–301.
- Nitsche MA, Jaussi W, Liebetanz D, Lang N, Tergau F, Paulus W. Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology* 2004; 29: 1573–8.
- Nitsche MA, Lampe C, Antal A, Liebetanz D, Lang N, Tergau F, et al. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. *Eur J Neurosci* 2006; 23: 1651–7.
- Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clin Neurophysiol* 2003b; 114: 2220–2.
- Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000; 527: 633–9.
- Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 2001; 57: 1899–901.
- Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol* 2005; 568: 291–303.
- Nowak DA, Grefkes C, Dafotakis M, Eickhoff S, Küst J, Karbe H, et al. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Arch Neurol* 2008; 65: 741–7.
- Nyffeler T, Cazzoli D, Wurtz P, Lüthi M, von Wartburg R, Chaves S, et al. Neglect-like visual exploration behaviour after theta burst transcranial magnetic stimulation of the right posterior parietal cortex. *Eur J Neurosci* 2008; 65: 741–7.
- Oliveri M, Bisiach E, Brighina F, Piazza A, La Bua V, Buffa D, et al. rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. *Neurology* 2001; 57: 1338–40.
- Pascual-Leone A, Gomez-Tortosa E, Grafman J, Alway D, Nichelli P, Hallett M. Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe. *Neurology* 1994; 44: 494–8.
- Paulus W. Transcranial direct current stimulation (tDCS). *Suppl Clin Neurophysiol* 2003; 56: 249–54.
- Payne BR, Lomber SG, Rushmore RJ, Pascual-Leone A. Cancellation of visuospatial lesion-induced spatial neglect. *Exp Brain Res* 2003; 150: 395–8.
- Pourtois G, Vandermeeren Y, Olivier E, de Gelder B. Event-related TMS over the right posterior parietal cortex induces ipsilateral visuo-spatial interference. *Neuroreport* 2001; 12: 2369–74.
- Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. *Neuroreport* 1998; 9: 2257–60.
- Priori A, Mameli F, Cogiamanian F, Marceglia S, Tiriticco M, Mrakic-Spota S, et al. Lie-specific involvement of dorsolateral prefrontal cortex in deception. *Cereb Cortex* 2008; 18: 451–5.
- Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. *J Neurophysiol* 1965; 28: 166–85.
- Ragert P, Vandermeeren Y, Camus M, Cohen LG. Improvement of spatial tactile acuity by transcranial direct current stimulation. *Clin Neurophysiol* 2008; 119: 805–11.
- Rush S, Driscoll DA. Current distribution in the brain from surface electrodes. *Anesth Analg* 1968; 47: 717–23.
- Sack AT, Hubl D, Prvulovic D, Formisano E, Jandl M, Zanella FE, et al. The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex for visuospatial functions. *Brain Res Cogn Brain Res* 2002; 13: 85–93.
- Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M, et al. Dynamics of language reorganization after stroke. *Brain* 2006; 129: 1371–84.
- Schenkenberg T, Bradford DC, Ajax ET. Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology* 1980; 30: 509–17.
- Schweid L, Rushmore RJ, Valero-Cabré A. Cathodal transcranial direct current stimulation on posterior parietal cortex disrupts visuo-spatial processing in the contralateral visual field. *Exp Brain Res* 2008; 186: 409–17.
- Shindo K, Sugiyama K, Huabao L, Nishijima K, Kondo T, Izumi S. Long-term effect of low-frequency repetitive transcranial magnetic stimulation over the unaffected posterior parietal cortex in patients with unilateral spatial neglect. *J Rehabil Med* 2006; 38: 65–7.
- Silva S, Basser PJ, Miranda PC. Elucidating the mechanisms and loci of neuronal excitation by transcranial magnetic stimulation using a finite element model of a cortical sulcus. *Clin Neurophysiol* 2008; 119: 2405–13.
- Sparing R, Dafotakis M, Meister IG, Thirugnanasambandam N, Fink GR. Enhancing language performance with non-invasive brain stimulation—a transcranial direct current stimulation study in healthy humans. *Neuropsychologia* 2008; 46: 261–8.
- Sparing R, Mottaghy FM. Noninvasive brain stimulation with transcranial magnetic or direct current stimulation (TMS/tDCS)—from insights into human memory to therapy of its dysfunction. *Methods* 2008; 44: 287–348.
- Sprague JM. Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat. *Science* 1966; 153: 1544–7.
- Sturm W, de Simone A, Krause BJ, Specht K, Hesselmann V, Radermacher I, et al. Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia* 1999; 37: 797–805.
- Talelli P, Greenwood RJ, Rothwell JC. Exploring Theta Burst Stimulation as an intervention to improve motor recovery in chronic stroke. *Clin Neurophysiol* 2007; 118: 333–42.
- Talelli P, Rothwell J. Does brain stimulation after stroke have a future? *Curr Opin Neurol* 2006; 19: 543–50.
- Thimm M, Fink GR, Küst J, Karbe H, Sturm W. Impact of alertness training on spatial neglect: a behavioural and fMRI study. *Neuropsychologia* 2006; 44: 1230–46.
- Thut G, Nietzel A, Pascual-Leone A. Dorsal posterior parietal rTMS affects voluntary orienting of visuospatial attention. *Cereb Cortex* 2005; 15: 628–38.
- Vallar G, Perani D. The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia* 1986; 24: 609–22.
- Vallar G, Rusconi ML, Bignamini L, Geminiani G, Perani D. Anatomical correlates of visual and tactile extinction in humans: a clinical CT scan study. *J Neurol Neurosurg Psychiatry* 1994; 57: 464–70.
- Varga ET, Elif K, Antal A, Zimmer M, Harza I, Paulus W, et al. Cathodal transcranial direct current stimulation over the parietal cortex modifies facial gender adaptation. *Ideggyogy Sz* 2007; 60: 474–9.
- Vines BW, Schneider NM, Schlaug G. Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. *Neuroreport* 2006; 17: 1047–50.
- Vuilleumier P, Hester D, Assal G, Regli F. Unilateral spatial neglect recovery after sequential strokes. *Neurology* 1996; 46: 184–9.
- Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. *Annu Rev Biomed Eng* 2007; 9: 527–65.
- Wassermann EM, Grafman J. Recharging cognition with DC brain polarization. *Trends Cogn Sci* 2005; 9: 503–5.
- Weiss PH, Rahbari NN, Hesse MD, Fink GR. Deficient sequencing of pantomimes in apraxia 2008; 70: 834–40.
- Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, et al. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke* 2005; 36: 1759–63.
- Ziemann U. TMS and drugs. *Clin Neurophysiol* 2004; 115: 1717–29.
- Ziemann U, Meintzschel F, Korchounov A, Ilić TV. Pharmacological modulation of plasticity in the human motor cortex. *Neurorehabil Neural Repair* 2006; 20: 243–51.
- Zimmermann P, Fimm B. Test Battery for Attention Performance (TAP). Wuersele, Germany: Psytest; 1995.