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Neglect-like effects induced by tDCS modulation of posterior parietal cortices in healthy subjects

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Background
Repetitive transcranial magnetic stimulation (rTMS) over right posterior parietal cortex was shown to induce interference on visuospatial perception in healthy subjects. Transcranial direct current stimulation (tDCS) is another noninvasive brain stimulation technique that works modulating cortical activity. It is applied through easy to use, noncostly, and portable devices.

Objective/Hypothesis
The aim of the current study was to investigate if the novel approach of "dual" stimulation over parietal cortices compared with the unilateral (right) cathodal one is able to induce greater and/or longer-lasting neglect-like effects in normal subjects performing a computerized visuospatial task.

Methods
Eleven healthy subjects underwent a computerized visuospatial task requiring judgments about the symmetry of prebisected lines in baseline condition, during and after tDCS. Right cathodal and left anodal tDCS were simultaneously applied over homologue posterior parietal cortices in the "dual" approach, whereas right cathodal tDCS was used in the traditional unihemisphere stimulation.

Results
A significant rightward bias in symmetry judgments as compared with baseline and sham conditions was observed in both the stimulation approaches. With "dual" tDCS compared with cathodal stimulation the effect was stronger and appeared earlier, but no longer-lasting after effects were found.

Conclusions
We speculate that the resulting modulation of interhemispheric inhibition mediated the additional rightward bias in task performance for "dual" hemisphere compared with unihemisphere tDCS.

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If "dual" tDCS may better reproduce mechanisms underlying real lesions, it could provide a more suitable model for rehabilitation of negligent patients.

Keywords visuospatial perception; noninvasive brain stimulation; cortical activity; line length judgment task

The term "hemispatial neglect" refers to the defective ability of patients to report, response, or orient to novel or meaningful stimuli presented to the opposite side of a brain lesion.[1]

Recent evidences from neuroimaging and brain stimulation studies suggest that a wide bilateral circuitry of interconnected cortical and subcortical areas of frontal and parietal cortices is involved in visuospatial attention in humans.[2-4]

The clinical evidence, further supported in noninvasive radiologic technique and neurophysiologic studies, converges on the supramarginal gyrus of the right inferior parietal lobule as a critical brain region involved in every case of neglect.[5-7] Moreover, these areas, particularly the intraparietal sulcus (IPS), are critically involved in line bisection task, a task commonly used to assess visuospatial functions.[8,9]

However, so far the basic mechanisms subserving unilateral space perception still remain obscure.

Lesions of the right hemisphere are far more likely to lead to severe and enduring neglect than left hemisphere damage.[10]

The hemispheric asymmetry of spatial unilateral neglect may be explained by the assumption that the right cerebral hemisphere possesses a largely bilateral representation of space and may readily direct spatial attention toward either side of space with a contralateral bias, although a more effective processing ability.[11] The left hemisphere, by contrast, is mainly concerned with the contralateral right side of space, with a minor representation of the ipsilateral side.[12,13] Most studies on spatial attention mechanisms in humans were based on the different tasks' performance of unilaterally brain-damaged patients. This approach, however, presents several conceptual and practical limitations. Further data have been provided by models of visuospatial neglect induced in healthy subjects through noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS).[3,14-16] TMS is able to produce focal, transient disruption of cortical function in normal humans during the performance of cognitive tasks so determining localized "reversible lesion."[17] Fierro et al.[15] first showed that rTMS trains delivered over posterior right parietal cortex during a visuospatial task were able to induce transitory neglect in healthy subjects. Further TMS studies confirmed the role of right posterior parietal cortex in visuospatial attention also increasing knowledge on more specific issues like timing of cortical activity,[3] far versus near space attention,[18] perceptual versus motor components of neglect.[14] Recently, another noninvasive technique of brain stimulation based on direct currents (transcranial direct currents stimulation, tDCS) has been used to modulate regional brain activity. The effects of tDCS that acts by altering the membrane potential of neurons are determined by the polarity of stimulation: anodal stimulation increases excitability and cathodal stimulation decreases excitability.[19-21] tDCS has been principally used to study cognitive functions and also to evaluate its potential in therapeutical application.[22,23] Indeed, anodal tDCS of the right parietal cortex has been recently found to ameliorate visuospatial neglect in 15 patients with right brain damage.[24] More recently, Sparing et al.[25] applied in separate sessions anodal, cathodal, or sham tDCS stimulation to the left or right posterior parietal cortices (PPCs) of both healthy controls and negligent patients. Authors found that in healthy subjects anodal tDCS applied over the right or left PPC biased visuospatial attention toward the contralateral hemispace with an opposite effect after cathodal tDCS; in negligent patients both anodal tDCS of the lesioned PPC and cathodal tDCS of the unlesioned PPC ameliorated the visuospatial deficit. Similar evidence of the role of cathodal tDCS in modulation of visuospatial performance comes from experimental animal studies.[26]

Recently the novel approach of "dual" stimulation has been applied on the motor cortex.[27] In this study, the authors applied simultaneously anodal tDCS to the nondominant motor cortex and cathodal tDCS to the dominant motor cortex to improve finger-sequence performance of the nondominant hand when compared with traditional unihemisphere stimulation (applying only anodal tDCS to the nondominant motor cortex). Vines speculates that the resulting modulation of interhemispheric inhibition mediated the additional improvement in finger-sequence performance for "dual" hemisphere compared with unihemisphere tDCS. The aim of the current study was to investigate if the novel approach of "dual" stimulation over parietal cortices compared with the unilateral (right) cathodal one is able to induce greater and/or longer lasting neglect-like effects in normal subjects performing a computerized visuospatial task.

This experimental design could also provide a pathophysiologic model of visuospatial neglect, exploring in particular the hypothesis of interhemispheric rivalry, according to which lesion of right parietal cortex (underlying left neglect) leads to hyperexcitability of the homologue contralateral area.[28,29]

Materials and methods

We studied 11 right-handed normal volunteers (five men, six women) aged 31.8 ± 6.9 with no evidence of brain dysfunction. We examined their performance on a computerized visuospatial task at various times: before tDCS

(T0: baseline condition); during tDCS (T1: 5 minutes, T2: 10 minutes after the start of stimulation); and after tDCS (T3: immediately after, T4: 5 minutes after the end of stimulation). Subjects were comfortably seated on a chair at a reading distance in front of a 15-inch 4:3 computer screen (33 cm wide and 25 cm high). The subject's seat was positioned so that eye level was at the middle of the display monitor that was centered on his/her sagittal midplane.

The experimental procedure was conducted according to Helsinki Declaration, approved by the ethical committee of our Department and all subjects gave their informed consent to participate in the experiment.

tDCS

One saline-dampened electrode (rectangular in shape, with area = 16.3 cm^2) was positioned over the right parietal cortex, centered on P6 of the 10-20 International EEG system and was set as cathodal; the other one (anodal) was positioned over the left parietal region, centered on P5 for "dual" stimulation or over the contralateral orbita as reference electrode, for cathodal stimulation. This location for the reference electrode has been shown to be functionally ineffective in experimental designs.[30]

Stimulation sites were selected according to our previous rTMS work[3] in which they were found to correspond to a region near the intraparietal sulcus. In the "real" stimulation condition the electrode over the right parietal cortex (P6) was used as the cathode, and the electrode over the left parietal cortex (P5) was the anode. A battery-driven, constant current stimulator (Magstim Company Ltd, Whitland, Wales, UK) delivered the electrical current from anode to cathode. The tDCS current ramped up during the first few seconds to a maximum of 1 mA, and then remained on for the remainder of the 15-minute stimulation period. This resulted in a total current density of 0.07 mA/cm^2 over the PPCs. To control unspecific effects of "dual" tDCS we performed an ineffective, "sham" stimulation positioning the electrode on the same sites on the scalp . The sham control condition was identical to the "dual" hemisphere condition, except that after 30 seconds, the experimenter reduced the current to zero and maintained it to zero until the end of the stimulation period. Participants reported for both real and sham tDCS a tingly or itchy sensation at the start of the stimulation, which faded away after a few seconds.

Visual stimulation

Visual stimuli consisted of black 1 mm thick horizontal lines transected by a 1 mm thick and 1 cm long vertical bar, presented on a white background with the transector exactly coincident with the center of the screen. Five lines were presented, differing in the position of the transector (at midpoint, rightward, or leftward) and in the overall length of the line and of its right and left segments (Figure 1). Tachistoscopic stimulus presentation of 50 milliseconds duration was used to prevent eye scanning. Before stimulus presentation the patient was required to fixate a central target (a black "*" character) that disappeared after 250 milliseconds, as soon as the visual stimulus was flashed. The software used for the aim was Psyscope X.[31] After the presentation of the stimulus the subject made a forced-choice decision about the respective length of the two segments with three response possibilities: equal, longer right or longer left, by pressing as soon as possible the corresponding colored key on a validated device (Psyscope ButtonBox, New Micros, Dallas, TX). Visual stimulation was given in baseline condition (T0), during (T1, T2), and after (T3,T4) tDCS in five separate blocks, each of them lasting about 90 seconds. In each block, subjects were given 30 trials in random order, 10 with line 1 and five with lines 2-5. Cathodal, "dual," and sham parietal stimulation were delivered in the same subjects on different days, with at least 1-week interval, by using the same experimental procedure. The order of the different stimulation conditions ("sham", "cathodal", "dual") was randomized across subjects.

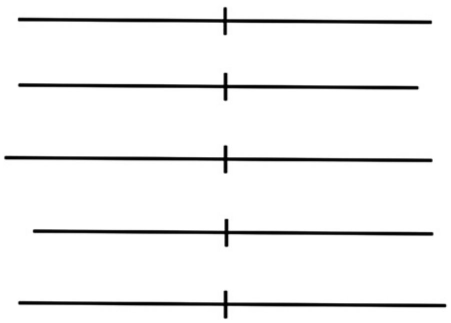

Figure 1 Visual stimuli presented to the subjects. For each stimulus, subjects made a forced choice decision of "equal," "longer right," and "longer left." Line 1: right segment, 75 mm; left segment, 75 mm (exactly bisected); line 2: right segment 70 mm; left segment, 75 mm (left elongated); line 3: right segment, 75 mm; left segment, 80 mm (left elongated); line 4: right segment, 75 mm; left segment, 70 mm (right elongated); line 5: right segment, 80 mm, left segment, 75 mm (right elongated).

The performance of the subjects on each trial was scored as follows: 0, correct response; 1, right segment of line 1 judged longer, or left and right segments of lines 2 and 3 judged equal (rightward bias); −1, left segment of line 1 judged longer, or left and right segments of lines 4 and 5 judged equal (leftward bias); 2, right segment of lines 2 and 3 judged longer (rightward bias); −2, left segment of lines 4 and 5 judged longer (leftward bias).

Mean scores at visuospatial task in each block of the experimental conditions were obtained for each subject; mean scores obtained during real (cathodal, "dual") and sham tDCS were then standardized subtracting the raw mean value from baseline.

Paired Students *t* test was used to compare baseline performance among the different conditions.

Analysis of variance (ANOVA) for repeated measures was performed to compare performance in tDCS conditions each

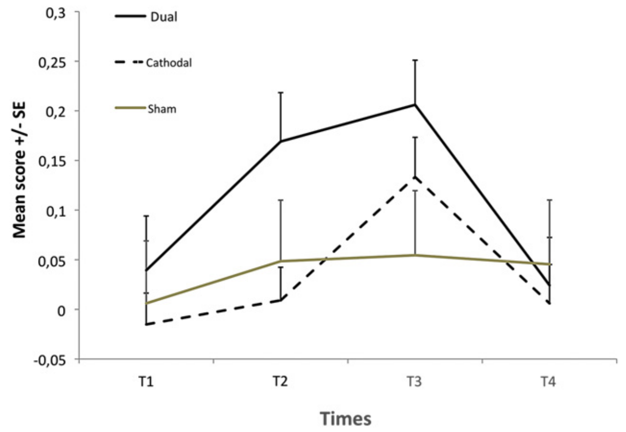

Figure 2 Mean scores (expressed as differences with respect to baseline) of dual, cathodal, and sham tDCS conditions at different times.

time with condition (3 levels: cathodal, "dual", sham) and time (4 levels: T1, T2, T3, T4) as within subjects factors.

We also computed errors toward right (+1, +2) and left (−1, −2) and expressed them as percentage of the number of trials for each experimental condition.

Comparisons of error percentage in each condition were performed through ANOVA for repeated measures with error type (2 levels: toward right and toward left) and conditions (13 levels: baseline [T0], cathodal tDCS [T1, T2, T3, T4], "dual" [T1, T2, T3, T4], and sham tDCS [T1, T2, T3, T4]) as within subjects factors.

Results

In baseline (T0 time) subjects showed a leftward bias in each experimental condition (mean score ± SE: cathodal −0.148 ± 0.067; "dual" −0.154 ± 0.065; sham –0.139 ± 0.037).

No significant differences in baseline performance were observed among conditions.

As concerns comparisons of performance scores with cathodal, "dual," and sham tDCS, ANOVA for repeated measures showed significant main effect of Time $F(3,30) = 11.48$; $P < .0000$ and a significant interaction time × condition $F(6,60) = 3.88$; $P < .005$ (Figure 2). Post hoc analysis showed that cathodal tDCS induced significant rightward bias at T3 time compared with all other times and to sham ($P < .001$), whereas with "dual" tDCS, the rightward bias was significant at T2 and T3 times compared with T1 and T4 times and with sham ($P < .005$). During "dual" tDCS, the performance resulted significantly shifted toward right at T2 ($P < .0005$) and T3 ($P < .05$) compared with cathodal stimulation. Moreover, post hoc analysis showed no significant changes in visual task performance during and after sham stimulation.

ANOVA for error percentages showed significant main effects for error type: $F(1,9) = 7.56$; $P < .0225$ and for the interaction condition × error type: $F(12,108) = 2.60$; $P < .0045$ (Figure 3). As evidenced by post hoc analysis, in baseline, subjects performed more errors toward left ($P < .0005$). The "dual" tDCS at times T2 and T3 induced a significant reduction of leftward errors compared with baseline ($P < .0001$) together with an increase, though not significant, of errors toward right. Significant reduction of leftward errors was induced also by cathodal tDCS at time T3 with no

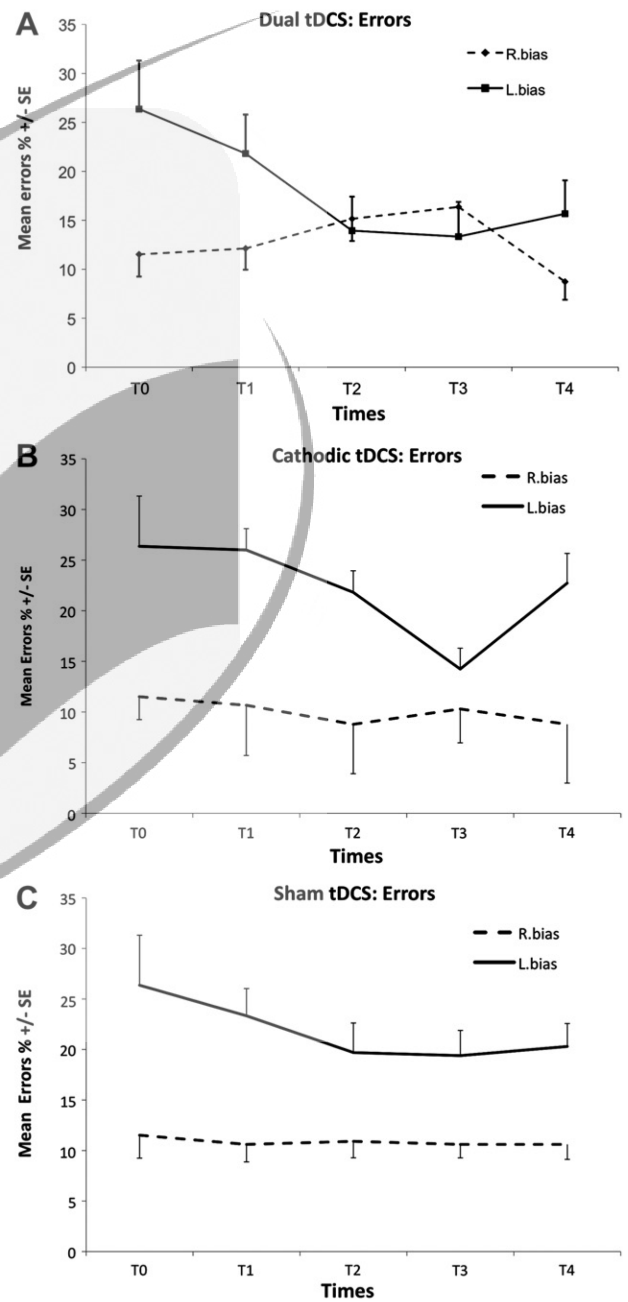

Figure 3 Mean percentage of leftward and rightward errors in baseline and at different times of tDCS: dual (**A**), cathodal (**B**), sham (**C**).

change in the rightward errors. No significant changes in left or rightward errors were induced by sham tDCS.

Discussion

The line bisection task has been extensively used to assess asymmetric allocation of spatial attention: subjects affected by right parietal damage and spatial neglect, estimate, or perceive the left segment as shorter and the right one as longer than their real size.[32] On the contrary, in our result all normal subjects showed a leftward bias in baseline condition, in fact, it is known that the general population tends to overestimate the left hemispace. The phenomenon is known as pseudoneglect[33] and interpreted as due to the physiologic hemispheric imbalance in visuospatial attention control.[34] This finding has been confirmed in a large meta-analysis study of bisection performance.[35]

After "real" "dual" or cathodal tDCS, subjects significantly changed their lateralization bias, reversing it to the right, as a "virtual left neglect." These results paralleled those previously obtained with rTMS on the right parietal cortex.[15]

Transient hyperpolarization of right PPC by cathodal tDCS, and synchronous depolarization of the left one in "dual" stimulation condition seems able to affect visuospatial behavior of normal subjects inducing a rightward bias that counteracted the physiologic pseudoneglect. This was also shown by the analysis of errors that evidenced a significant reduction of leftward errors with both stimulation approaches compared with baseline and sham condition.

After real "cathodal" tDCS, a significant effect was present after 15 minutes of stimulation, whereas after "dual" tDCS, the effect appeared earlier (after 10 minutes of stimulation), but in both cases it was completely over 5 minutes after the end of stimulation. The latency to obtain a relevant bias is probably due to the time the direct current needs to induce polarity changes sufficient to disrupt visuospatial processing that seems to be reached earlier by "dual" stimulation. To our knowledge, this is the first application of "dual" tDCS to explore visuospatial function. Concerning monopolar parietal tDCS, our results are in agreement with previous works in humans and animals that reported significant effects in visuospatial task performance on contralateral hemispace both during and immediately after the end of the monopolar stimulation.[25,26] In both studies, the effect was over at later evaluation times. However, different stimulation sites and parameters used in these studies as well as the different time points explored do not allow detailed comparisons with our results.

Moreover, it should be noticed that studies investigating the "time course" of tDCS effects on the motor cortex gave also nonunivocal results. In particular, a study measuring variations of motor evoked potential (MEP) size recorded from 0 to 20 minutes after turning off tDCS, interestingly showed a "fluctuating" pattern of effectiveness of both cathodal and anodal tDCS with a significant change on MEP size 1 and 15 minutes after anodal and 0 and 5 minutes after cathodal tDCS.[36]

Indeed, in the current study, we found similar effects by using both stimulation approaches. According to Vines et al.[27] with "dual" tDCS the effect was stronger and appeared earlier, but no lasting after effects were found.

This "time limited" effect we found could follow the peculiar network organization of a strongly lateralized function, as the visuospatial one, even if the role of the stimulation parameters used has to be taken into account.

The stronger and earlier effect of the "dual" stimulation could be explained by data deriving from studies in which a damaged cortical asymmetric function is often associated to the hyperactivity of the contralateral homologue area.[28] This contralateral hyperactivation can of course be considered as compensatory and seems to support the hypothesis of a maladaptive "dead-end strategy"[16,37] because of the interhemispheric rivalry. On this basis, one could argue that effects of "dual" tDCS may better reproduce mechanisms underlying real lesions, so providing a more suitable model for rehabilitation of negligent patients.

In the current study, the lack of effects of sham stimulation and the "time course" of the effects during and after tDCS seems to exclude unspecific effects on the cognitive performance. A rightward bias is likely due to learning effect, responsible for a potential reinforcement of task performance, could be taken into account, although lack of significant changes among times in sham condition seems to rule out this evidence.

In conclusion, our data, if confirmed by more and larger series, may provide a rationale to use "dual" tDCS as a useful complementary tool to investigate distributed asymmetric cognitive functions where interhemispheric rivalry plays a critical role. Further studies are worth performing to define optimal stimulation parameters for a long-lasting and efficient modulation with the opportunity of therapeutical applications.

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