Short Communication

Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices

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ARTICLE ABSTRACT

We used single-pulse transcranial magnetic stimulation (TMS) to study visuospatial attention. TMS was applied over one hemisphere, or simultaneously over both the right and left posterior parietal cortex (PPC), at two different interstimulus intervals (ISI) during a visual detection task. Unilateral TMS over the right and left PPC, respectively, impaired detection of contralateral presented visual stimuli at an ISI of 150 ms. By contrast, simultaneous biparietal TMS induced no significant changes in correct stimulus detection. TMS at an ISI of 250 ms evoked no changes for magnetic stimulation over either the right or the left parietal cortex. These results suggest that both PPC play a crucial role at a relatively early stage in the widely distributed brain network of visuospatial attention. The abolition of behavioral deficits during simultaneous biparietal TMS underlines the common hypothesis that an interhemispheric imbalance might underlie the disorders of neglect and extinction seen following unilateral brain damage.

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It is well established that the parietal lobe plays a central role in the widely distributed brain network of visuospatial attention. Behavioral studies have shown that patients with unilateral parietal lesions may exhibit a wide spectrum of neuropsychological deficits, including visual neglect. In recent years, research has convincingly shown that the disorder of neglect can be dissociated into several symptoms. These symptoms can selectively affect different sensory modalities, cognitive processes, spatial domains and coordinate systems (Halligan et al., 2003). The phenomenon of extinction represents one of these symptoms. Patients with extinction respond appropriately to unilateral stimuli in either hemispace, but, on bilateral stimulation, the stimulus contralateral to the lesion remains undetected, although perception of single stimuli in either visual hemifield is preserved (Halligan et al., 2003; Vallar, 1998). The classic model of hemispheric rivalry (Kinsbourne, 1977) has provided a neural explanation for extinction in so far that both parietal lobes may exert reciprocal interhemispheric inhibition. Hence, presentation of a competing stimulus activating

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the intact hemisphere leads to further suppression of the lesioned hemisphere.

Previous functional neuroimaging studies (PET, fMRI) have revealed a detailed network of areas involved in visuospatial attention (e.g. prefrontal, basal ganglia, reticular formation, thalamus, cingulate) and have confirmed the important role of the parietal cortex (e.g. Fink et al., 1997; Fink et al., 2000; Halligan et al., 2003; Nobre et al., 1997). However, fMRI and/or PET activation in a certain brain area during a task does not prove a priori that this area is functionally relevant to this task. In recent years, numerous studies have demonstrated that TMS is capable of confirming the functional relevance of an activation due its ability to interfere actively with brain function. TMS has become especially helpful in establishing temporal relationships and in examining the functional connectivity between brain regions (Pascual-Leone et al., 2000). In normal volunteers, rTMS to the parietal lobe can induce selective extinction, leading to contralateral omissions in the visual detection of simultaneously presented double stimuli (Pascual-Leone et al., 1994). Furthermore, repetitive TMS (rTMS) of the left or of the right parietal lobe impairs the detection of stimuli in the opposite hemisphere, whereas the subjects’ attention to ipsilateral targets is improved (Hilgetag et al., 2001). In patients with neglect caused by stroke, rTMS of the unaffected hemisphere transiently improved contralateral neglect and extinction (Brighina et al., 2003; Oliveri et al., 2001).

The results of these previous TMS studies are consistent with the hemispheric rivalry hypothesis (Kinsbourne, 1977) and are in line with the findings of animal studies, which indicate that the posterior parietal cortex plays an important role in visual spatial attentional mechanisms. Studies using a method of reversible cooling deactivation in cats have especially demonstrated that unilateral deactivation of the posterior parietal cortex results in contralateral neglect. Moreover, this visual hemineglect could be reversed by additional deactivation of the same region in the opposite hemisphere (Lomber and Payne, 1996; Payne et al., 2003).

We applied parietal TMS in single-pulse mode in healthy volunteers at two different time points. Additionally, we investigated directly the prediction of paradoxical contralateral lesions from the hemispheric rivalry model using biparietal simultaneous TMS stimuli. We hypothesized that the TMS effects induced by unilateral magnetic stimulation might be abolished by applying additional contralateral TMS.

In all experiments, subjects correctly identified catch trials to a high degree (mean correct response 92% ± 5%). Subject’s performance in detecting catch trials during the application of real TMS (correct response: 91% ± 6%) was not significantly different from that of the corresponding trials with sham TMS (correct response rate: 94% ± 4%, P > 0.05, Student’s paired t test).

For reaction times, repeated-measures analysis of variance (ANOVA), with site of TMS (3 levels: P3 vs. P4 vs. P3 + P4) and visual stimulus (3 levels: left vs. right vs. bilateral) as within-subject factors demonstrated no significant main effects and interactions. Mean reaction time averaged for all conditions was 487 ± 13 ms (visual stimuli left: 470 ± 12 ms; right: 483 ± 12 ms; bilateral: 522 ± 22 ms).

Correct response rates of real TMS conditions were compared separately to the corresponding sham conditions, and relative changes in subjects’ performance were computed consecutively for each subject. A repeated-measures analysis of variance (ANOVA), with site of TMS (3 levels: P3 vs. P4 vs. P3 + P4) and site of visual stimulus (3 levels: left vs. right vs. bilateral) as within-subject factors indicated a main effect of site of TMS (F(2,18) = 7.24, P < 0.01). To further explore differences between single factors, a two-tailed t test was used as post-hoc test. Significance level was adjusted to P < 0.01 using Bonferroni’s correction. These contrasts indicated that TMS over P4 influenced the detection of contralateral visual stimuli (left: −12% ± 0.03; bilateral: −13% ± 0.06, P < 0.008). However, the detection of ipsilateral presented visual stimuli showed a non-significant trend towards deterioration (−9% ± 0.03, P = 0.03) (Fig. 1).

On the contrary, TMS over P3 impaired only visual detection of visual stimuli, which were presented in the right (contralateral) visual hemifield (−13% ± 0.06) (Fig. 1). More detailed analysis of wrong answers for bilateral visual stimuli showed a significantly increased number of reported right visual stimuli, when TMS was delivered over P4 (P = 0.021) (Fig. 2). This indicates that the left stimulus of a bilateral stimulus pair went undetected, pointing towards contralateral extinction. Analysis of wrong answers for bilateral visual stimuli during TMS over P3 did not reveal such pattern.

TMS at 250 ms post-stimulus evoked no significant changes in the detection rate for magnetic stimulation over either the right or the left parietal cortex (Fig. 3).

Unilateral TMS over P3 or P4, respectively, impaired the detection of contralateral visual stimuli at an ISI of 150 ms. By contrast, no significant changes in performance were seen for neither unilateral nor bilateral presented visual stimuli following simultaneous stimulation of both parietal lobes (P3 + P4) (Fig. 4).

TMS over the parietal cortex significantly impaired detection of contralateral visual stimuli during unilateral and, to a lesser degree, during bilateral stimuli. These effects were more pronounced for right hemispheric TMS. The present results demonstrate that single-pulse TMS is generally capable of transiently disrupting the function of the parietal cortex, similar to the studies which applied trains of TMS pulses (Brighina et al., 2003; Hilgetag et al., 2001; Oliveri et al., 2001; Pascual-Leone et al., 1994). Our results provide further evidence that both parietal lobes are functionally involved in visuospatial attention. However, TMS over the right posterior parietal cortex induced much stronger effects, which is consistent with both clinical findings (Pedersen et al., 1997) and evidence from functional neuroimaging studies (Fink et al., 2001; Vallar, 1998). A previous TMS study in healthy volunteers found a similar involvement of both parietal lobes with right-hemispheric dominance in a visual detection task (Hilgetag et al., 2001). Nevertheless, TMS studies investigating visuospatial attention reported contradictory results regarding right hemispheric dominance: a study investigating visual detection found mirror-symmetric commensurate TMS effects for
both hemispheres (Pascual-Leone et al., 1994), whereas a study investigating line bisection found effects only following stimulation of the right parietal cortex (Fierro et al., 2000). We found that parietal TMS impaired the processing of visuospatial attention at 150 ms post-stimulus, whereas TMS at 250 ms had no effect. A similar time frame for parietal processing of visuospatial attention was also found by a TMS study using a line bisection task (Fierro et al., 2001). Studies with event-related potentials which investigated the modulation of visual processing by spatial attention have indicated a similar time course. They suggested a gain control over information flow, starting at about 80 ms, and with a parietal N1 component peaking at 150–160 ms (Hillyard and Anllo-Vento, 1998). These findings suggest that the parietal cortex is involved in visuospatial attention during a relatively early stage of visual processing. However, further investigations, which apply single-pulse TMS at a number of different ISIs, would be needed to provide more detailed information about the timing of visuospatial attention in the human brain.

In our study, we did not observe any effects of single-pulse TMS on ipsilateral visual stimulus detection, although previous studies could demonstrate that parietal TMS may lead to an increased sensitivity to ipsilateral sensory stimuli (Hilgetag et al., 2001; Seyal et al., 1995). It is most likely that differences in methodology (single-pulse instead of
repetitive TMS) account for the lack of this effect in our study. However, it has been reported that sham TMS with a coil tilted away from the head does not simulate the exact sensory perception as with the real stimulation (Loo et al., 2000). The authors investigated the effects of TMS with a figure-of-eight-shaped coil held in various positions over the motor cortex and measured motor evoked potentials (MEP) and the subjective TMS sensations. None of the positions met the criteria for an optimal sham, and arrangements associated with a higher likelihood of scalp sensation were more likely to stimulate the cortex and to evoke MEPs. Alternatively, we could have applied TMS over “inactive” brain regions. However, the caveat with stimulation of “control areas” in this setting is that potential projected effects of TMS over areas, which are far from the active areas (e.g., posterior parietal cortex), cannot be ruled out (Paus, 1999). In our study, the induction of a second transient ‘virtual lesion’ by simultaneous biparietal TMS led to the abolition of behavioral deficits induced by unilateral magnetic stimulation. This novel finding fits well with the hemispheric rivalry explanation (Kinsbourne, 1977). One prediction of the rivalry hypothesis is that lesions in one hemisphere cause disinhibition of homologous areas in the unimpaired hemisphere and thus result in enhanced awareness of the ipsilesional hemispase. This pattern was found in patients with right-hemispheric brain damage, who actually showed better reactions to right-sided than to central stimuli (Ladavas, 1990; Smania et al., 1998). A second prediction of the rivalry model is that a second contralateral lesion should restore interhemispheric balance with consequent recovery of the attention deficit. This prediction has been confirmed in a patient with sequential strokes: a first right parietal stroke induced a severe contralateral hemineglect, which disappeared after a second stroke involving the left hemisphere (Vuilleumier et al., 1996). The most famous example for the observation that brain damage occasionally can result in a return of a previously compromised ability is known as the Sprague effect. In cats, Sprague observed such restoration following a massive ablation of visual areas in one hemisphere and a subsequent lesion of the contralateral superior colliculus (Sprague, 1966). Furthermore, studies using a method of reversible cooling deactivation in cats could clearly demonstrate that visual hemineglect, induced by unilateral deactivation of the posterior parietal cortex, could be reversed by additional deactivation of the homologue areas in the opposite hemisphere (Lomber and Payne, 1996; Payne et al., 2003).

It is noteworthy that previous TMS studies could only induce either neglect (Fierro et al., 2000; Fink et al., 2001) or extinction (Hilgetag et al., 2001; Pascual-Leone et al., 1994). This might relate to the finding that the anatomical correlates of extinction in right-brain-damaged patients do not entirely overlap with those of neglect (Halligan et al., 2003; Karnath et al., 2003). Further studies could evaluate this hypothesis by using differential TMS over these areas during a visuospatial attention task.

Finally, our results underline the important role of the posterior parietal cortex in visual neglect and extinction. Our results may provide direct evidence in support of the theory of hemispheric rivalry in visuospatial attention. The recent discovery of a complete reversal of an existing lesion-induced neglect by means of cooling deactivation in cats (Payne et al., 2003) together with the finding of an amelioration of attentional deficits in stroke patients using parietal TMS contralateral to the lesions (Brighina et al., 2003; Oliveri et al., 2001) may provide a theoretical basis for development of therapeutic strategies concerning the rehabilitation of neglect patients.

Ten subjects (mean age 23.9 ± 3.3 years) participated in the study after giving written informed consent. All subjects were right-handed, had normal or corrected to normal vision and had no history of neurological abnormalities. The protocol was approved by the local Institutional Review Board. Subjects were seated in a comfortable chair placed in front of a PC monitor (21”, 75 Hz, viewing distance 60 cm) in a dimly illuminated room. Stable viewing was supported through a chin-rest. Subjects were instructed to keep fixation on the center throughout the experiment. Eye movements were monitored by a second experimenter. However, the very eccentric location of the stimuli made any appearance of
target saccades very unlikely. None of the trials had to be eliminated because of significant eye movements, although some subjects needed a few training trials to achieve stable fixation. Small black dots of $2 \times 2, 2 \times 3, 3 \times 3, 3 \times 4$ or $4 \times 5$ pixels were presented at approximately $23^\circ$ eccentricity left or right of the center of the screen against a white background. After an initial block presenting all trial sizes, two individual perithreshold sizes were chosen separately for each subject’s hemifield to avoid floor and ceiling effects. The 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. This procedure of stimulus titration was adopted from a previous study (Hilgetag et al., 2001).

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