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HEMIEXTINCTION INDUCED BY TRANSCRANIAL MAGNETIC STIMULATION OVER THE RIGHT TEMPORO-PARIETAL JUNCTION

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Abstract—Whereas it is widely accepted that the parietal cortex is crucial for visual attention, the role of the temporal cortex and the temporo-parietal junction (TPJ) is less clear. There are clinical reports of patients with lesions in different posterior temporal areas which exhibit contralateral visual neglect but this syndrome seems to be less frequent than in patients with parietal lesions. In a previous study, we could show that single-pulse transcranial magnetic stimulation (TMS) over the right inferior parietal cortex is capable to induce both neglect-like and extinction-like impairments of performance in normal subjects. In the present study, we used this method to examine the functional role of the superior temporal gyrus (STG) and the TPJ of the right hemisphere for visuo-spatial attention. Healthy volunteers were asked to detect small dots appearing for 40 ms unilaterally on right or left side or bilaterally on a computer screen. TMS was applied over the TPJ or STG. TMS over the TPJ induced an extinction-like behavioral pattern to the contralateral hemifield. TMS over the STG had no effect. The results demonstrate a functional involvement of the TPJ in visuo-attentional processing of competing stimuli in both hemifields. This region is part of the cortical network mediating stimulus-driven attention which is relevant for processing of competing stimuli.

Key words: extinction, TMS, attention, temporo-parietal junction.

Although the clinical syndrome of hemineglect is mainly attributed to lesions of the inferior parietal lobe, there are clinical data which indicate that lesions of other cortical sites also induce attentional deficits. Especially the role of the superior temporal cortex for attention is currently under debate (Marshall et al., 2002; Halligan et al., 2003; Karnath et al., 2001). There are clinical reports of patients with lesions in different posterior temporal areas which exhibit contralateral visual neglect but this syndrome seems to be less frequent than in patients with parietal lesions. Two recent studies sought to specify the role of the superior temporal cortex within the network of spatial perception: Hillis et al. (2005) found that in patients with lesions of the superior temporal gyrus (STG) object-centered neglect is more frequent, whereas a TMS study (Ellison et al., 2004) found that STG is crucial for visual search. Several studies assign the temporo-parietal junction (TPJ) a crucial role for selective visual attention (Halligan et al., 2003); lesions in this area are possibly associated with hemiextinction phenomena (Karnath et al., 2003).

Hemiextinction reflects the inability to perceive a stimulus in the presence of a competing stimulus in the contralateral visual field; in contrast, neglect denotes an inability to attend to stimuli or part of stimuli even when there is no competing stimulus. Both syndromes are associated (Milner and McIntosh, 2005).

The present study used transcranial magnetic stimulation (TMS) to explore the role of the STG and the TPJ for attention. Several recent studies used TMS to investigate the cortical representation of attention. These studies mainly focused on the posterior parietal cortex showing that TMS can induce neglect-like (Fierro et al., 2000, 2001) and extinction-like (Hilgetag et al., 2001; Pascual-Leone et al., 1994) behavioral deficits. In a study from our laboratory (Dambeck et al., 2006) we could show that single-pulse TMS over P4 induces both neglect- and extinction-like behavioral patterns which are abolished when a simultaneous stimulus is applied at P3 supporting the hemispheric rivalry hypothesis (Kinsbourne, 1977). In this study, shortly presented eccentric small black dots had to be detected. Extinction was present when detection of one of two dots simultaneously appearing within both hemifields was abolished and neglect denoted the missing detection of dots presented unilaterally.

In the present study TMS was applied to the right TPJ and the STG using the same paradigm. Because both clinical findings (Pedersen et al., 1997), TMS studies (Chambers et al., 2004) and functional neuroimaging studies (Fink et al., 2001; Vallar, 1998) indicate a right hemispheric dominance for attentional processes, we focused on right temporal stimulation.

EXPERIMENTAL PROCEDURES

Subjects

Fourteen subjects participated in the study (eight males, six females, mean age (24.7±1.8 [S.D.] years) All subjects were right-handed according to the Edinburgh Inventory (Oldfield, 1971), had normal or corrected to normal vision and had no history of neurological abnormalities. The protocol was approved by the local institutional review board and all subjects gave their written informed consent.

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Abbreviations: ANOVA, analysis of variance; PPC, posterior parietal cortex; STG, superior temporal gyrus; TMS, transcranial magnetic stimulation; TPJ, temporo-parietal junction.

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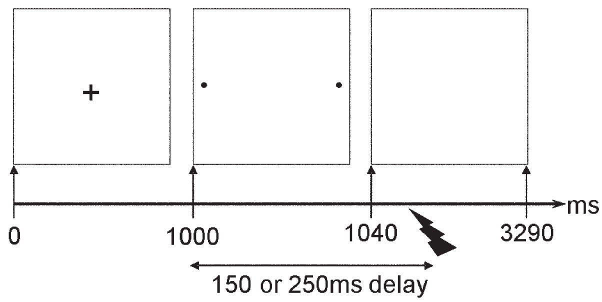

Fig. 1. Outline of the time course of the experiment.

Visual stimuli

Small black dots of 2×2, 2×3, 3×3, 3×4, or 4×5 pixels were presented on a computer screen against white background (pixel resolution 1024×768, 75 Hz, viewing distance 60 cm). The dots appeared 182 mm to the left or to the right of a central fixation cross (visual eccentricity approximately 23° left or right of the center of the screen). During an initial block dots of each size appeared; afterward two dot sizes were chosen for each subject for the following experiments to avoid floor and ceiling effects.

In addition, empty catch trials were presented to detect those subjects who erroneously reported absent visual stimuli. Subjects used their right hand to report the detection of stimuli via mouse click: index finger on the left mouse button for unilateral left visual stimuli, ring finger on the right mouse button for unilateral right stimuli and middle finger on the middle mouse button for bilateral stimuli. At the beginning of each trial a central fixation cross appeared for 1000 ms. The stimuli were then presented for 40 ms. Subjects then had a 2250 ms time interval for response click (total trial length 3290 ms). In every block, left, right and bilateral stimuli for both sizes as well as catch trials were shown 20 times in random order (total of 140 trials). The time course of the experiment is shown in Fig. 1. Eye movements and blinks were monitored by a second experimenter. The experimental setup with eccentric location of the stimuli in the visual field combined with the short presentation time made saccades toward the stimuli unlikely. Prior to the pilot session (determination of dot size) a few training trials were done in order to familiarize subjects with the experiment. None of the trials had to be eliminated due to blinks or eye movements.

TMS

We used two Magstim 200 magnetic stimulators equipped with figure-of-eight-shaped coils (diameter 9 cm for each wing). TMS was applied over right TPJ and STG as determined by individual MRI data using a stereotactic system for TMS application (Fa. Localite, Bonn, Germany) (Fig. 2). The determination of the TPJ stimulus site followed the criteria provided by Mort et al. (2003) in their study of brain lesions in neglect patients: As TPJ we defined the region within a triangle linking the origin of the ascending posterior segment of the lateral fissure, the intersection of a vertical line dropped from this point and the superior temporal sulcus, and the origin of the ascending posterior segment of the superior temporal sulcus. The STG site was situated on the STG ventral to the sulcus centralis. The TMS coil was oriented with the handle in posterior–medial direction. Single-pulse magnetic stimuli at an intensity of 60% maximum stimulator output at two time intervals (150 ms and 250 ms) after visual stimulus onset were applied. As control, TMS was administered at the same stimulation sites holding the coil perpendicular to the scalp (sham stimulation). The order of conditions (TMS time interval, real/sham TMS) was counterbalanced across subjects.

Statistical analysis

The average number of correct responses and average reaction times for all experimental conditions were computed separately for each subject for left, right and bilateral visual stimuli. These data were analyzed using a repeated-measures analysis of variance (ANOVA) with "TMS" (real, sham), "site of TMS" (TPJ, STG), "site of visual stimulus" (right, left, bilateral) and "TMS onset time" (150 ms, 250 ms) as within-subject factors. Post hoc *t*-tests were applied in case of significance.

In addition, wrong answers for bilateral stimuli were further analyzed to detect extinction-like behavior. If subjects detected only the left visual stimulus following a bilateral presentation, this reflected a failure to perceive the right visual stimulus and vice versa. Thus, the number of wrongly reported left and right answers for bilaterally presented visual stimuli reflected extinction to the right and left side, respectively. These data were analyzed using Student's *t*-test, for all analyses the threshold of significance was set to $P<0.05$.

RESULTS

In all experiments, subjects correctly identified catch trials to a high degree, TMS had no influence on catch trial identification (mean correct response 98.2% all sham stimulation experiments, 97.6% all real stimulation experiments, $P>0.5$, Student's *t*-test).

For reaction times, repeated-measures ANOVA, with "TMS" (real, sham), "site of TMS" (TPJ, STG), "site of visual

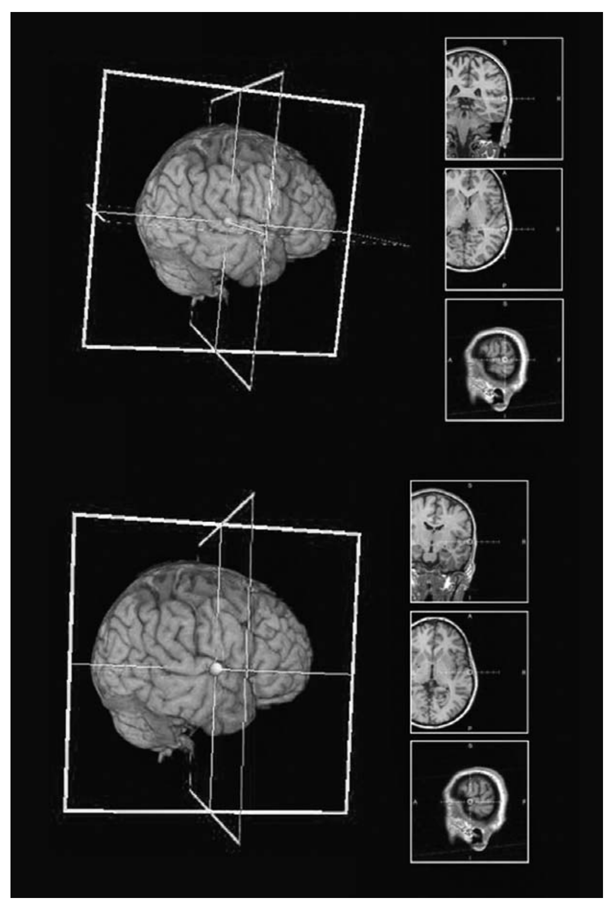

Fig. 2. Example of the brain regions stimulated with TMS in one subject. Above, TPJ, bottom, STG.

stimulus" (right, left, bilateral) and "TMS onset time" (150 ms, 250 ms) as within-subject factors demonstrated no significant main effects and interactions. Mean reaction time averaged for all conditions was 462.7 ms (sham stimulation: 460.4 ms, real stimulation: 465.0 ms).

Numbers of correct responses of real TMS conditions were compared separately to the corresponding sham conditions. A repeated-measures ANOVA, with "TMS," "site of TMS," "TMS onset time" and "site of visual stimulus" as within-subject factors revealed a significant interaction of the factors "TMS," "site of visual stimulus" and "site of TMS" ($P=0.019$). Post hoc *t*-tests showed that there was a significant deterioration of correct detection of bilateral stimuli after real TMS (compared with sham TMS) over the TPJ (sham TMS in average $n=31.4\pm1.1$ S.E. correct responses, real TMS $n=28.2\pm1.2$ S.E., $P=0.0001$) (Fig. 3). Results of all other post hoc *t*-tests were not significant (average number of correct responses±S.E., TMS over TPJ: sham TMS 32.8±1.1 (stimuli left), 33.3±0.9 (stimuli right), real TMS 32.1±1.1 (stimuli left), 33.4±0.8 (stimuli right), TMS over STG: sham TMS 34.2±0.9 (stimuli left), 34.2±0.8 (stimuli right), 31.6±1.0 (stimuli bilateral), real TMS 34.1±1.0 (stimuli left), 32.9±0.9 (stimuli right), 30.9±1.1 (stimuli bilateral)). Whereas TMS over both STG and TPJ only slightly impaired detection of unilateral stimuli on either side, there was a great deterioration in correct judgment of bilateral stimuli after TMS applied to the TPJ. The same task was only mildly impaired after TMS over the STG. Thus the significant interaction of visual stimulus site and TMS stimulation site was mainly due to the differential effect of TMS over STG and TPJ on judgment of bilateral stimuli.

More detailed analysis of wrong answers for bilateral visual stimuli showed a significantly increased number of reported right visual stimuli, if TMS was delivered over TPJ ($P=0.001$, Student's *t*-test, comparison of the number of bilateral stimuli which were incorrectly judged as unilateral right stimuli with real vs. sham TMS). Data of the two time points of TMS stimulation were collapsed as there was no differential effect of TMS stimulus time in the ANOVA analysis (Fig. 4). This indicates that the left stimulus of a bilateral stimulus pair went undetected, which could be the behavioral correlate of an extinction phenomenon. TMS over STG did not induce an extinction-like behavior. Also, there was no such increase for bilateral stimuli judged as unilateral left for this condition.

DISCUSSION

The present study found that TMS over the right TPJ induces an extinction effect to the left visual hemifield, whereas TMS over the right STG has no differential effect on detection of bilateral stimuli. During unilateral stimulus presentation, TMS over TPJ induced a slight amelioration of detection of ipsilateral stimuli, whereas detection of contralateral stimuli was unimpaired.

The results of the present study extend the results of previous TMS studies on the functional representation of attention (Dambeck et al., 2006; Chambers et al., 2004; Ellison et al., 2004; Hilgetag et al., 2001). These previous reports did not investigate the role of TPJ or STG in the attentional/representational network processing competing stimuli in both hemifields but focused on neglect-like phenomena and visual search. It has been shown that TMS over the angular gyrus induces attentional dysfunction (Chambers et al., 2004). rTMS over the posterior parietal cortex is able to elicit an extinction effect (Hilgetag et al., 2001) and a neglect-like behavioral pattern in a landmark task (Ellison et al., 2004). A patient study using intraoperative cortical stimulation (Thiebaut de Schotten et al., 2005) found that line bisection is impaired both for STG stimulation and stimulation of the supramarginal gyrus. A previous study from our group using the same experimental setup with TMS application to the posterior parietal cortex (PPC) found an effect leading both to a neglect-like

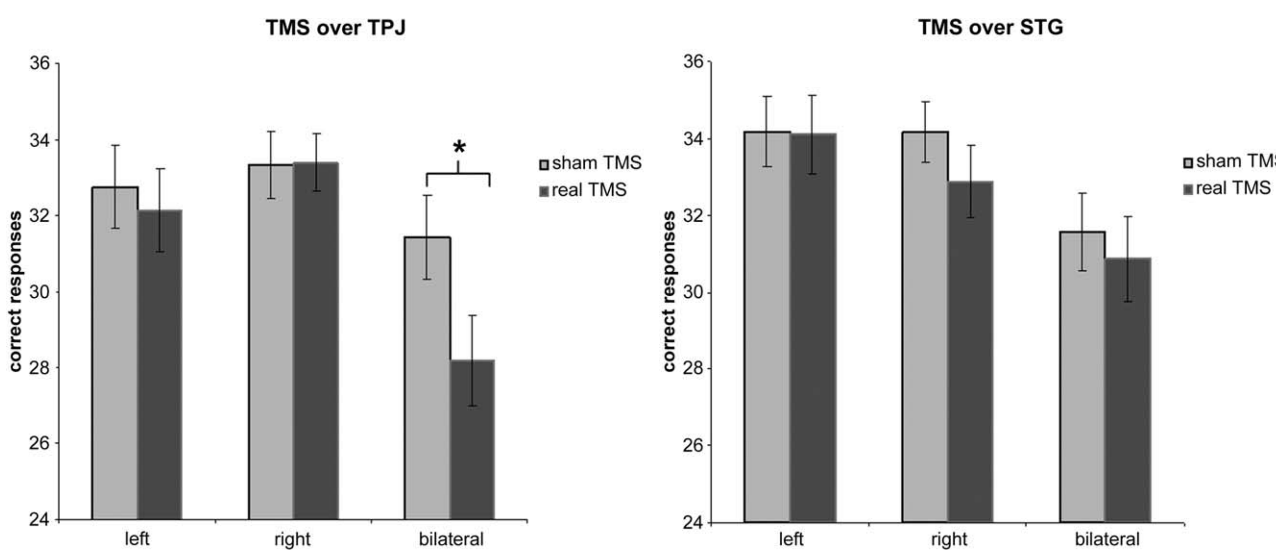

Fig. 3. Comparison of the differential effects of real and sham TMS on correct detection of unilateral and bilateral stimuli. Left, stimulation over the TPJ, right, stimulation over the STG. Data are pooled from both time points of TMS stimulation (150 ms and 250 ms after stimulus onset). Real TMS over the TPJ induced a deterioration of detection of bilateral stimuli compared with sham TMS (* $P=0.0001$). Error bars indicate standard error.

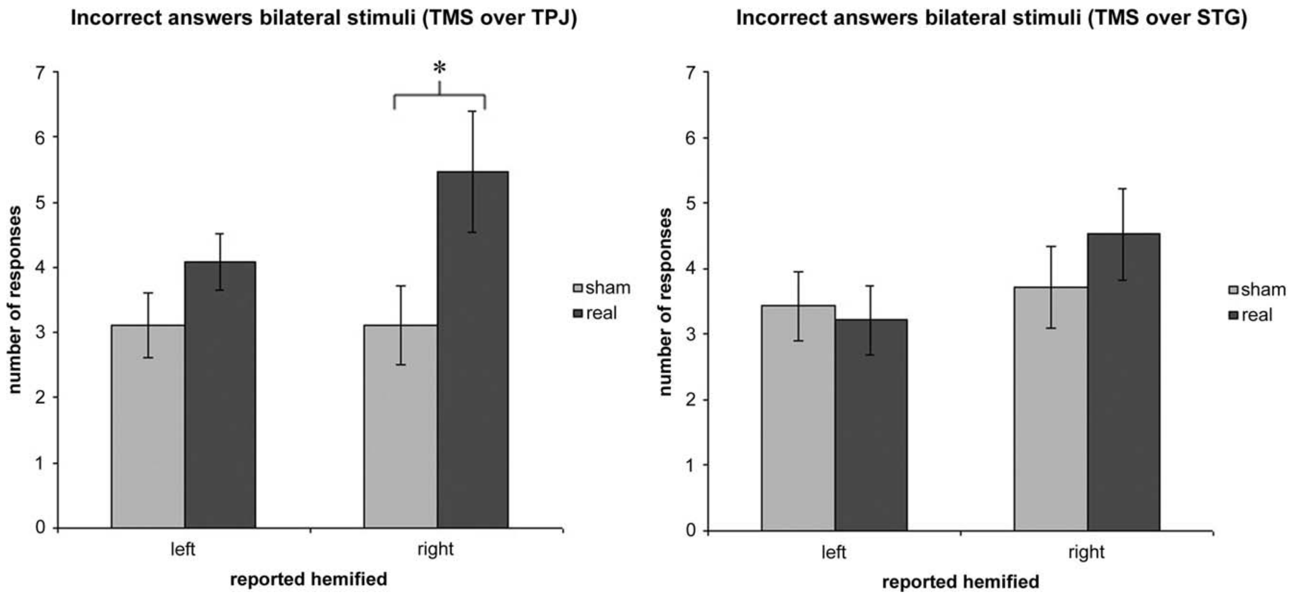

Fig. 4. Analysis of number of incorrect responses following presentation of bilateral stimuli with real or sham TMS. Data are pooled from both time points of TMS stimulation (150 ms and 250 ms after stimulus onset). Real TMS over TPJ (left) induced an increase in unilateral right judgments following bilateral stimulus presentation compared with sham TMS (* $P=0.001$); subjects missed the simultaneously presented stimulus on the left side (hemiextinction to the left side). TMS over STG (right) had no significant effect. Error bars indicate standard error.

behavioral pattern and to an extinction phenomenon on the contralateral side (Dambeck et al., 2006). In this study, bilateral TMS over PPC was able to abolish the effects of unilateral TMS, consistent with the hemispheric rivalry hypothesis (Kinsbourne, 1977).

Whereas the previous studies clearly could demonstrate a modulatory effect of TMS over the posterior parietal cortex on attention, the results regarding the TPJ are less clear. Although this region seems to play a crucial role for attentional processes (Halligan et al., 2003; Thiebaut de Schotten et al., 2005), a previous study focusing on neglect-like behavior did not find effects of TMS over the supramarginal gyrus on attention (Chambers et al., 2004). In accordance, the present study did not find an effect of TMS over the TPJ on unilaterally presented stimuli. However, we could demonstrate a hemiextinction which is present only after stimulation of TPJ but not of the adjacent STG. Although neglect and extinction phenomena are largely associated in patients, there is a subgroup of patients which show extinction but no neglect (Vallar et al., 1994). Extinction is more frequent in subcortical lesions involving the white matter (Vallar et al., 1994); a recent study claimed that the TPJ is critical for extinction (Karnath et al., 2003).

The TPJ is part of the system of stimulus-driven attention within the framework proposed by Corbetta and Shulman (2002), which is involved in attentional shifts induced by stimuli at unattended locations (Kincade et al., 2005). The activations of extrastriate regions due to exogenous stimuli in the study of Kincade et al. (2005) fit with the network described for processing of competing stimuli in visual hemifields (Fink et al., 2000). Although the findings of the present study do not provide evidence for a preferential activation of the stimulus-driven attentional system during detection of bilateral stimuli, we speculate that the detection of stimuli presented bilaterally may require a more unfocused attentional state than the detection of unilateral stimuli; thus, a TMS-induced modulation of the system processing stimulus-driven attention may become more critical for detection of bilateral concurrent stimuli. Indirect support for this notion comes from investigations of patients showing visual extinction: recent studies reported that the extent of extinction critically depended on the relative salience of the bilaterally presented stimuli (Geeraerts et al., 2005; Vuilleumier and Rafal, 2000).

The results of the ANOVA analysis did not show a differential effect of stimulus time of TMS over the TPJ. Thus, we assume that the time window of the critical involvement of the TPJ in bilateral stimulus processing lies between 150 ms and at least 250 ms. Possibly related to our results are reports of event-related potential studies on attentional processes, which found a N170 component related to involvement of fusiform areas in stimulus detection (Vuilleumier et al., 2001; Hillyard and Anllo-Vento, 1998) and later frontal components (Kennett et al., 2001). According to recent studies, the N170 component is not the first stage of visual stimulus processing in the parieto-frontal network: the frontal eye-field is involved in visual search during an earlier time window of 40–80 ms (O'Shea et al., 2004) and the temporo-parietal region is active during face processing during the same early time window (Pourtois et al., 2005). However, a recent EEG study reported that the N170 component may be the critical component for processing of competing stimuli (Corentin and Rossion, 2006).

TMS over the superior temporal cortex did not elicit significant effects on attentional processing, consistent with previous TMS studies (Ellison et al., 2004; Pascual-Leone et al., 1994). This negative result provides no direct evidence against an involvement of this region in attentional processes but does not support the view that the STG is the center of the attentional network. A recent study suggests that the superior temporal cortex is mainly involved in object-centered attentional processes (Hillis et al., 2005) which were not tested here.

CONCLUSION

In conclusion, the present study showed that TMS over the TPJ induces an extinction-like behavioral pattern, whereas TMS over the STG had no effect on the attentional processes tested here. The results indicate an involvement of the TPJ, which is part of the ventral frontoparietal network, in attentional processing of competing visual stimuli.

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