**Imaging the Brain Activity Changes Underlying Impaired Visuospatial Judgments: Simultaneous fMRI, TMS, and Behavioral Studies**

Damage to parietal cortex impairs visuospatial judgments. However, it is currently unknown how this damage may affect or indeed be caused by functional changes in remote but interconnected brain regions. Here, we applied transcranial magnetic stimulation (TMS) to the parietal cortices during functional magnetic resonance imaging (fMRI) while participants were solving visuospatial tasks. This allowed us to observe both the behavioral and the neural effects of transient parietal activity disruption in the active healthy human brain. Our results show that right, but not left, parietal TMS impairs visuospatial judgment, induces neural activity changes in a specific right-hemispheric network of frontoparietal regions, and shows significant correlations between the induced behavioral impairment and neural activity changes in both the directly stimulated parietal and remote ipsilateral frontal brain regions. The revealed right-hemispheric neural network effect of parietal TMS represents the same brain areas that are functionally connected during the execution of visuospatial judgments. This corroborates the notion that visuospatial deficits following parietal damage are brought about by a perturbation of activity across a specific frontoparietal network, rather than the lesioned parietal site alone. Our experiments furthermore show how concurrent fMRI and magnetic brain stimulation during active task execution hold the potential to identify and visualize networks of brain areas that are functionally related to specific cognitive processes.

**Keywords:** functional magnetic resonance imaging, parietal cortex, simultaneous TMS-fMRI, transcranial magnetic stimulation, visuospatial processing

**Introduction**

The execution of visuospatial tasks (Haxby et al. 1991; Ungerleider and Haxby 1994; Cohen et al. 1996; Goebel et al. 1998; Trojano et al. 2000; Sack, Sperling, et al. 2002) as well as visuospatial imagery (Mellet et al. 1996; Trojano et al. 2000; Sack, Hubl, et al. 2002) leads to increased activations in the frontoparietal cortices of the human brain, particularly the intraparietal sulcus region of both hemispheres (Formisano et al. 2002; Trojano et al. 2002). Previous functional brain imaging results suggest a direct positive relationship between increased cognitive demand, as reflected in visuospatial task difficulty, and underlying parietal activity (Tagaris et al. 1996; Carpenter et al. 1999; Ng et al. 2001; Vannini et al. 2004).

However, although functional brain imaging provides evidence for transient local activity changes during the execution of specific perceptual and cognitive processes, it does not permit inferences about causal structure–function relationships. Such inferences can only be made based on a controlled manipulation of brain activity whose impact on behavior or cognition can be quantified. The technique of transcranial magnetic stimulation (TMS) is a well-established tool for inducing transient disruptions of neural activity (“virtual lesions”) non-invasively in human volunteers (Hallett 2000; Pascual-Leone et al. 2000; Walsh and Cowey 2000; George et al. 2002; Sack 2006).


Our group previously showed that, although functional brain imaging reveals bilateral parietal activity during the execution of visuospatial tasks, only right parietal TMS significantly perturbs behavioral performance (Sack, Sperling, et al. 2002; Sack et al. 2005). This right-hemispheric dominance of parietal cortex for visuospatial functions as determined by TMS (for review, see Rushworth and Taylor 2006) also parallels neuropsychological findings of hemispatial neglect after unilateral parietal damage (Vallar et al. 1996).

This conclusion, however, is based on the implicit assumption that the TMS-induced behavioral impairments are indeed caused by TMS-induced local neural activity disruptions at the stimulation site of TMS. However, recent TMS studies indicate that short bursts of focal TMS might not exclusively affect neural activity directly under the stimulation coil, but extends its neural consequences to remote and interconnected brain regions (Bohning et al. 2000; Civardi et al. 2001; Paus 2002; Bestmann et al. 2004; Daskalakis et al. 2004; Denslow et al. 2005; Pleger et al. 2006; Ruff et al. 2006; Taylor et al. 2007).

A comprehensive picture of such remote activity changes can only be acquired by measuring task-related neural activity concurrently, that is, during the application of TMS. Following the pioneering work of Paus (TMS and positron emission tomography [PET], Paus et al. 1997; see also Fox et al. 1997) and Bohning (TMS and functional magnetic resonance imaging...
Simultaneous fMRI and TMS during Spatial Judgments

Eight male right-handed healthy participants (mean age \( \pm \text{SD} = 31.3 \pm 4.6 \)) with normal or corrected-to-normal vision without past neuropsychiatric history took part according to procedures approved by the local ethics committee. Prior to the experiment, informed consent was obtained from all participants. Participants were unaware of the purposes and predictions of the experiments until after test completion. All participants had previous experience with participating in TMS and fMRI measurements; 4 participants were already familiar with receiving TMS inside the MR scanner. None of the participants reported any adverse effects of the simultaneous TMS and fMRI measurements.

Materials and Methods

Participants

Eight male right-handed healthy participants (mean age \( \pm \text{SD} = 31.3 \pm 4.6 \)) with normal or corrected-to-normal vision without past neuropsychiatric history took part according to procedures approved by the local ethics committee. Prior to the experiment, informed consent was obtained from all participants. Participants were unaware of the purposes and predictions of the experiments until after test completion. All participants had previous experience with participating in TMS and fMRI measurements; 4 participants were already familiar with receiving TMS inside the MR scanner. None of the participants reported any adverse effects of the simultaneous TMS and fMRI measurements.

Magnetic Resonance Imaging

MRI was performed at 3 T (Siemens TRIO, Erlangen, Germany) using a standard transmit-receive head coil. High-resolution anatomical images were acquired using a short echo-time magnetization-prepared rapid gradient-echo sequence (time repetition/echo time \([\text{TR}/\text{TE}] = 15/4\text{ ms, flip angle } 20^\circ, 1 \times 1 \times 1 \text{ mm}^3\) resolution) covering the whole head. Functional images (16 oblique contiguous slices) were obtained using a \( T_2^*\)-weighted single-shot gradient-echo planar imaging (EPI) sequence \([\text{TR}/\text{TE} = 2000/36\text{ ms, flip angle } 70^\circ, 96 \times 128\text{ matrix, frequency-selective fat suppression, } 2 \times 2 \text{ mm}^2\) resolution, 4 mm section thickness). Single volume acquisitions lasted 1440 ms (16 \times 90\text{ ms}), followed by a temporal gap of 560 ms. Participants wore earplugs and headphones for hearing protection whereas head motion was restricted using foam pads.

Transcranial Magnetic Stimulation

TMS was applied through a nonferromagnetic figure-of-eight coil (70 mm outer wing diameter, 2 windings of 10 turns each, inner winding diameter 53 mm, distance between outer coil surface and windings: 2-3 mm [variation due to manufacturing tolerance], coil inductance: 20 \( \mu \text{H} \) with a maximal current at 100% stimulator output of approximately 5 kA, initial rise time of biphasic pulse approximately 90 \( \mu \text{s} \)). The coil was additionally mechanically supported by an appropriately shaped 8 mm plastic former that was attached on the reverse side of the coil by high strength fiber tape (The Magstim Company, Whitland, Wales, UK). The coil was connected to a Magstim Rapid stimulator (The Magstim Company) outside the radiofrequency (RF) shielded cabin via an 8-m cable through an RF filter tube. TMS pulses were applied at an intensity of 100% maximum output and synchronized with the beginning of each new EPI volume acquisition by use of a 5-V transistor-transistor logic (TTL) pulse. We decided to use a fixed stimulation intensity for all participants instead of individual motor-threshold-related intensities because previous studies indicated that the motor threshold is not an appropriate measure for dosing stimulation intensity above nonmotor areas (e.g., Stewart, Walsh, Rothwell 2001). Note, however, that the effective output intensity in this setup was 24% below a standard TMS setup (as measured by comparing our participants’ motor thresholds using the standard vs. MR-compatible Magstim 70 mm double coil), due to the resistive properties of the long connecting cable and slightly different coil characteristics (see also Bestmann et al. 2004; Ruff et al. 2006). In our subject sample, this fixed stimulation intensity corresponded to an average individual motor-threshold-related stimulation intensity of 126% and was thus comparable to those stimulation intensities used in previous parietal TMS studies investigating the same paradigm outside the MR scanner (Sack, Sperling, et al. 2002). Interactions of magnetic stimulation and MR image acquisition were avoided by applying 5 TMS pulses in the 560-ms period subsequent to each volume acquisition at a frequency of \(-13.3\text{ Hz} \) (i.e., at 1500, 1575, 1650, 1725, and 1800 ms). The remaining 200 ms period ensured that subsequent volume acquisition was unperturbed (Shastri et al. 1999; Bestmann et al. 2004).

TMS Localization

We determined the TMS target stimulation sites based on our previous fMRI findings using the identical paradigm as used in the current study (Sack, Sperling, et al. 2002; Sack et al. 2005). Concretely, we used fMRI group results from a different subject sample performing the exact same paradigm to initially guide our TMS target site localization. Based on these previous fMRI results of bilateral parietal activation during the execution of the visual clock paradigm, we applied frameless stereotaxy outside the MR scanner to identify which exact positions on the subjects’ scalp corresponded to the revealed left and right parietal activation clusters. This procedure revealed that the exact parietal activation clusters associated with this paradigm are located on average 1 cm posterior to P3 and P4 of the international 10–20 electrode positioning system. Please note that although this approach is based on group fMRI data of a different subject sample and does thus not represent an individual fMRI-based TMS neuronavigation, the fMRI data also revealed that the intersubject variability in parietal activation during this paradigm was rather low (see Sack, Sperling, et al. 2002). Based on these data, we decided to mark these locations (1 cm posterior to P3 and P4) as target sites.
to P3 and P4) on the head of each participant as TMS target sites in our current studies. We assumed that these target sites would represent the best a priori estimation of the optimal stimulation sites for the simultaneous TMS and fMRI measurements of the visual clock paradigm. Importantly, the reconstruction of the exact TMS coil position inside the MR scanner during the simultaneous TMS and fMRI measurements post hoc validated our assumption by revealing an appropriate placement of the TMS coil above the individual parietal activation sites in every individual participant. Hence, in accordance with these results, magnetic brain stimulation was applied inside the MR scanner by centering the TMS coil above the offline located and marked target positions with the coil producing an initial mediolateral current orientation. For a post hoc identification of the exact stimulated position of the TMS coil and the underlying cortical region, vitamin E capsules were attached to the plane of the TMS coil inside the MR scanner. The TMS coil center was estimated by triangulation between the vitamin capsules, and the exact position and orientation of the coil inside the scanner were reconstructed by a projection perpendicular to the tangential plane of the TMS coil center. Hence, by visualizing the reconstruction of the exact coil position relative to the simultaneously acquired anatomical and functional images of each participant, we were able to post hoc validate the cortical and functional region underlying the TMS coil.

**Simultaneously Combined TMS and fMRI**

After the TMS target stimulation site had been determined and marked outside the scanner, the TMS coil was placed and fixated above the parietal stimulation site inside the standard head coil of the MR scanner. In some cases, it was necessary that participants slightly tilted their head in order to allow accurate placement of the TMS coil. After the TMS coil had been placed above the target site inside the MR scanner, foam-padded cushions were used to firmly fixate both the participant’s head and the TMS coil in order to avoid head/coil movements as well as mechanical vibrations of the TMS coil during the measurement. Participants wore earplugs and noise-reducing headphones throughout the experiment.

The TMS coil was connected to the magnetic stimulator outside the RF-shielded MRI examination room via an 8-m-long cable through an RF filter tube near the rear end of the magnet. TMS pulses and MRI data acquisition were synchronized using a TTL (5 V) trigger signal generated at each RF excitation pulse. Millisecond triggering accuracy was ensured by specially developed C program that controlled the TMS stimulator.

For further details on the technical realization of simultaneously combined TMS and fMRI measurements, please see, for example, Bohning et al. (1997, 1999, 2000), Shastri et al. (1999), Bestmann et al. (2002, 2004), and Ruff et al. (2006).

**Cognitive Tasks**

Stimuli of the visual clock paradigm consisted of pictures of schematic timesheets with a yellow face and two white or yellow hands. Participants were instructed to press one out of 2 buttons whenever a target or nontarget stimulus appeared. Depending on the instruction, targets were defined as clocks with angles of 30° or 60° (angle discrimination task: ANGLE) or clocks with white hands (color discrimination task: COLOR). Subjects used their right index finger for indicating the detection of targets and their right middle finger for indicating the detection of nontarget stimuli. For every trial, we measured the response time from stimulus onset until button press. Stimuli were presented at central fixation with a duration of 300 ms and an interstimulus interval of 2000 ms. Stimuli were presented in the horizontal direction. The size of the stimuli was 10°/C210°/C176°/C176°/C176°. In order to also assess the temporal high-pass filtering to remove low-frequency nonlinear drifts of 5 or fewer cycles per time course, spatial smoothing with a Gaussian kernel (full width half maximum = 6 mm), and 3-dimensional motion correction to correct for small head movements by aligning all volumes to the first volume via rigid body transformations. Functional slices were coregistered to the anatomical volume and transformed into Talairach space.

The statistical analysis of the variance of the blood oxygen level-dependent (BOLD) signal was based on the application of multiple regridding analysis to the series of fMRI data (Friston et al. 1995). In the multisubject fixed effects analysis, the general linear model (GLM) of the experiment was computed from the z-normalized volume time courses. The signal values during the ANGLE and COLOR tasks with and without TMS as well as the TMS-only condition were considered the effects of interest.

The main effect of TASK was computed by contrasting the ANGLE task execution versus the COLOR task execution (regardless of TMS) and by color coding the results according to a blue-red scale; red indicating higher neural activity during the ANGLE compared with the COLOR task (Supplementary Fig. 2A). The main effect of TMS was computed by contrasting task execution with TMS versus task execution without TMS (regardless of task) and by color coding the results according to a blue-red scale; red indicating areas with significantly higher neural activity during task executions with TMS compared with those without TMS (Supplementary Fig. 2B). In order to also assess the impact of TMS independent of active task performance, we contrasted TMS during central fixation versus fixation without TMS (baseline), separately for both parietal stimulation sites (Supplementary Fig. 3). In the TMS during central fixation condition, no button press was required.

To determine TASK × TMS interaction effects, volume of interest (VOI) analyses were performed. VOIs were defined based on the computation of a multisubject multiple regression analysis of the main effect of TASK using the GLM framework. This contrast analysis revealed the regional activations associated with both task executions. The resulting fMRI activity map was thresholded at a t value corresponding to q(FDR) < 0.05 and a spatial extent threshold of 100 mm³. For each cluster
the main effect of TASK indicates that the ANGLE task required significantly longer RTs compared with the COLOR task, the significant TASK × TMS interaction statistically ensures that the revealed task-dependent behavioral effects of right parietal TMS were not confounded by a priori difficulty or baseline differences between both tasks. The difference in RT increase between both tasks was thus also significant (Fig. 1A).

Similar to the RT data, we also analyzed the accuracy differences between the different conditions. Although the analyses failed to reach statistical significance, the results are descriptively in accordance with the task-dependent effect of right parietal TMS. Although the average error rate in the ANGLE task increased from 2.13 false responses without TMS to 3.62 false responses during right parietal TMS, the accuracy level for the COLOR task remained unaffected (2.6 false responses without TMS vs. 2.0 false responses during TMS).

Neural Effects of Right Parietal TMS
When comparing BOLD signal changes during task execution with versus without right parietal TMS, we found significant TMS-induced BOLD signal reductions in the right SPL (stimulated), the right postcentral gyrus, and the right MFG during the ANGLE task whereas no such effect was observed for the

Results

Regional Brain Activities during Task Execution without TMS
The analysis of fMRI signal changes during task execution compared with baseline revealed that both ANGLE and COLOR task execution resulted in an increase of neural activity in striate and extrastriate visual cortex, bilateral inferior parietal lobule (IPL) and bilateral superior parietal lobule (SPL), bilateral inferior frontal gyrus (IFG) and bilateral middle frontal gyrus (MFG), bilateral FEF, bilateral supplementary motor area (SMA), bilateral fusiform gyrus, and bilateral primary motor cortex (PMC) (see also Sack et al. 2003 and Roebroeck et al. 2005).

A direct statistical contrast analysis between ANGLE versus COLOR task execution regardless of TMS was computed in order to directly compare fMRI signal differences between both tasks. This main effect of TASK revealed a significantly stronger neural activity during the ANGLE compared with the COLOR task in the left and right occipital lobe, the left and right IPL, the left and right SPL, and the left and right MFG (Supplementary Fig. 2A).

Behavioral Effects of Right Parietal TMS
The mean RT of the angle task execution increased from 495 ms (standard error of the mean [SEM] = 32 ms) without TMS to 562 ms (SEM = 32 ms) during right parietal TMS, representing a significant TMS-induced RT increase of 67 ms. In contrast, the mean RT of the color task execution showed no change in RT from 552 ms (SEM = 18 ms) without TMS to 441 ms (SEM = 22 ms) during right parietal TMS. The inference statistical analyses of the RTs were based on a 2-way repeated measures ANOVA with the conditions TASK (ANGLE vs. COLOR) and TMS (with vs. without TMS) as within-subject factors. The analyses revealed a significant main effect of TASK (F1,7 = 16.339, P = 0.005), TMS (F1,7 = 5.581, P = 0.05) and a significant interaction between TASK and TMS (F1,7 = 6.393, P = 0.039). Post hoc simple contrast analyses revealed that only the RTs in the ANGLE task were significantly increased during right parietal TMS (t7 = 3.696, P = 0.008) whereas no significant RT change was found for the COLOR task (t7 = 0.516, P = 0.622). Note that although
COLOR task (Fig. 2). This difference in TMS-induced reduction of neural activity between both tasks was particularly pronounced in the right SPL and MFG (Fig. 2). Accordingly, a VOI 2-way ANOVA revealed a significant interaction between TASK (ANGLE vs. COLOR) and TMS (with vs. without) only in the SPL ($F = 2.418, P < 0.05$) and MFG ($F = 2.322, P < 0.05$) of the right hemisphere. Moreover, a significant correlation between the degree of activity reduction and the strength of the behavioral impairment was only found for the ANGLE task and only in the right SPL ($r = 0.91, P < 0.05$) and right MFG ($r = 0.89, P < 0.05$).

In contrast to these task-specific TMS-induced activity modulations, we also identified regions that did not show any task-specific differences in their reaction to TMS, including areas in the occipitotemporal and parietooccipital cortex. Bilateral SMA and right FEF showed a TMS-induced reduction that was of equal strength for both tasks, while the left and right auditory cortices showed no task-specific difference in their TMS-induced increase of neural activity caused by the discharge noise of the TMS coil (Siebner et al. 1999). Other brain regions, like for example, the superior occipital gyrus, showed similar neural activation levels during all experimental conditions and were thus independent of TASK or TMS.

When analyzing the TMS-induced BOLD signal changes during central fixation compared with baseline, only increased neural activity was observed in bilateral auditory cortex (discharge noise of the TMS coil), bilateral parietal operculum, and bilateral inferior central sulcus (Supplementary Fig. 3A). Whereas the former probably reflects the activation of bilateral secondary somatosensory cortex due to peripheral nerve stimulation, the latter is likely caused by contralateral peripheral muscle stimulation at the stimulation site of TMS.

**Study II: Imaging the Neural Effects of Left Parietal TMS during Active Visuospatial Judgments**

For the second fMRI experiment, the same participants were reinvited and tested again according to the same procedure (see Materials and Methods of Study I) as in the first fMRI experiment. However, unlike in the first experiment not the right but the left parietal cortex was stimulated during the TASK and TMS condition. This second study was conducted at least several weeks after the first measurements had been recorded.

**Results**

**Regional Brain Activities during Task Execution without TMS**

The analysis of fMRI signal changes during task execution compared with baseline revealed that both ANGLE and COLOR task execution resulted in an increase of neural activity in striate and extrastriate visual cortex, bilateral IPL and SPL, bilateral IFG and MFG, bilateral FEF, bilateral SMA, bilateral fusiform gyrus, and bilateral PMC. A direct statistical contrast analysis between ANGLE versus COLOR task execution was computed in order to directly compare fMRI signal differences between both tasks. This main effect of TASK revealed a significantly stronger neural activity during the ANGLE compared with the COLOR task in the left and right occipital lobe, the left and right IPL, the left and right SPL, and the left and right MFG. In sum, the regional brain activities during task execution without TMS were identical to the results revealed in Study I (Supplementary Fig. 2A).

**Behavioral Effects of Left Parietal TMS**

TMS-induced disruption of the left parietal cortex resulted in no behavioral performance changes in either task. The mean RT of the angle task execution was 530 ms (SEM = 31 ms) without TMS and 527 ms (SEM = 27 ms) during left parietal TMS. Similarly, the mean RT in the color task also hardly differed between no stimulation (454 ms) and left parietal TMS (456 ms). Hence, the RTs during left parietal TMS were almost identical to the RTs without TMS (Fig. 1B). Accordingly, the inference statistical analyses of the RTs within a 2-way repeated measures ANOVA only revealed a significant main effect of TASK ($F_{1,7} = 26.701$,
Neural Effects of Left Parietal TMS

When comparing BOLD signal changes during task execution with left parietal TMS to those without, we only found significant TMS-induced BOLD signal increases in bilateral auditory and predominantly right motor areas (Fig. 3). The left and right auditory cortices showed no task-specific difference in their TMS-induced increase of neural activity caused by the discharge noise of the TMS coil (Fig. 3). The increased motor cortex activity predominantly on the right side likely reflects the contralateral peripheral muscle stimulation at the stimulation site of TMS. The bilateral occipital cortex and the left and right SPL showed similar neural activation levels during all experimental conditions and thus independent of TASK or TMS. Importantly, none of the brain areas showed neither an interaction between TASK (ANGLE vs. COLOR) and TMS (with vs. without) nor a significant correlation between the TMS-induced changes in brain activity and changes in behavioral performances.

When analyzing the TMS-induced BOLD signal changes during central fixation compared with baseline, only increased neural activity was observed in bilateral auditory cortex, bilateral parietal operculum, and predominantly right central sulcus (Supplementary Fig. 3B).

Direct Statistical Comparison between Both Studies

We directly compared the behavioral results of both studies within a 3-way $2 \times 2 \times 2$ repeated measures ANOVA with the conditions TASK (ANGLE vs. COLOR), TMS (with vs. without TMS), and SITE (left parietal vs. right parietal stimulation) as within-subject factors. This analysis revealed a significant second-order interaction between TASK $\times$ TMS $\times$ SITE ($F_{1,7} = 6.572, P = 0.05$), indicating that the task-specific effect of TMS (impairing the angle task whereas leaving the color task unaffected) is statistically different between the left and right parietal stimulation site.

In order to also statistically compare the functional brain imaging results of both studies directly, we entered the fMRI data of each participant from both studies into one GLM. In the multishubject fixed effects analysis, the GLM of the experiment was computed from the z-normalized volume time courses of each run in each study. The multiple linear regression of the BOLD response time course was calculated for each voxel using 10 predictors: ANGLE and COLOR tasks with and without TMS, as well as the TMS-only condition, for the right and for the left parietal stimulation site. We conducted VOI-based GLM analyses in which VOIs were defined based on the computation of a multisubject multiple regression analysis of the main effect of TASK using the GLM framework. This contrast analysis revealed the regional activations associated with both task executions. The resulting fMRI activity map was thresholded at a $t$ value corresponding to $q$ (FDR) < 0.05 and a spatial extent threshold of 100 mm$^3$. For each cluster within this fMRI activity map, a VOI analysis was conducted testing for second-order interaction effects between TASK $\times$ TMS $\times$ SITE. The main effect of TASK contrast analysis thus served as an independent localizer for the subsequent VOI analyses in order to ensure a statistically independent selection criterion for defining the VOIs. We revealed a significant interaction between TASK (ANGLE vs. COLOR) $\times$ TMS (with vs. without) $\times$ SITE (left parietal vs. right parietal stimulation site) in right SPL ($t = 2.1, P = 0.05$), right postcentral gyrus ($t = 2.0, P = 0.05$), and right MFG ($t = 2.7, P = 0.01$). These fMRI interaction effects support the

Figure 3. Neural effects of left parietal TMS. Group fMRI results of task execution with versus without left parietal TMS, separately for ANGLE and COLOR tasks. Results are superimposed on the inflated hemispheres of the Montreal Neurological Institute template brain. All relevant activations can be seen from the lateral view. Blue indicates areas with a significantly reduced neural activity during task execution with TMS and red areas with a significantly increased neural activity induced by TMS. AC = auditory cortex, MC = motor cortex, STS = superior temporal sulcus, CS = central sulcus.
notion that within this specific right-hemispheric frontoparietal network, the neural effects of TMS are task dependent and significantly different between both stimulation sites. The asymmetry of behavioral effects between left versus right parietal virtual lesions is thus mirrored by an asymmetry of the respective neural consequences.

**Functional Connectivity Analyses**

In addition to the classical standard GLM fMRI analyses, we also computed functional connectivity maps in order to reveal the brain network of functional connectivity underlying both task executions. When using GCM to identify the network of brain areas that are functionally connected during the angle task execution, we found that the stimulated right SPL shows functional connectivity to a bilateral frontoparietal network including the SPL, postcentral, and MFG of both hemispheres (Fig. 4A, upper part). In contrast, the instantaneous GCM for the execution of the color task (Fig. 4A, lower part) as well as the instantaneous GCM for the TMS-only condition (data not shown) did not reveal this frontoparietal network of functional connectivity, indicating the specificity of this functional connectivity network for the visuospatial angle task.

Moreover, by defining the right parietal reference region for our GCM based on the GLM contrast angle task execution with versus without right parietal TMS, we identified the exact same network of brain areas using functional connectivity analyses as we revealed when mapping the task-specific TMS-induced activity modulations (Fig. 4B). This means that the identified direct and remote task-specific neural effects of right parietal TMS, that is, those brain areas that showed task-specific TMS-induced decreases of neural activity during angle task execution with TMS (Fig. 2), represent the same brain areas that are functionally connected during the execution of specifically this visuospatial task (Fig. 4B). Hence, the right SPL, right postcentral gyrus, and right MFG not only show visuospatial task-specific neural activity reductions during right parietal TMS (Fig. 2) but also represent the functional connectivity network underlying the execution of visuospatial judgments (Fig. 4). In contrast, the instantaneous GCM for the execution of the color task did not reveal this task-dependent frontoparietal network of functional connectivity, thereby mirroring the absence of color task-specific TMS-induced neural effects as revealed in the GLM analyses (Figs. 2 and 4A).

**Discussion**

Using the novel combination of concurrent TMS and fMRI, we show that TMS to right parietal cortex selectively impairs visuospatial judgments but not an appropriate control task that used identical visual stimuli. Critically, we were able to visualize the impact of this disruption on neural activity and show that a decrease in task performance is mirrored by a corresponding decrease of cortical activity not only at the site of parietal stimulation but also in remote and interconnected frontal brain regions of the same hemisphere.

Both visual tasks, angle, and color discrimination resulted in increased neural activity in parietal and frontal regions of both hemispheres (Supplementary Fig. 2A). However, only the magnetic manipulation of right parietal activity significantly impaired the behavioral performance in the ANGLE but not in the COLOR task (Fig. 1A). In contrast, TMS-induced disruptions of left parietal activity did not impair the behavioral performance of either task (Fig. 1B). These task- and hemispheric-specific behavioral effects of parietal TMS inside the MR scanner replicate previous findings outside the MR scanner. Hence, although participants were clearly aware that they were participating in a technically demanding experiment, this did not seem to have unduly confounded their performance, which replicated our previous findings using the same paradigm. In previous off-line TMS studies we demonstrated, based on a much larger sample size, that right parietal TMS significantly impaired performance in the angle, but not the color discrimination task, whereas left parietal TMS led to no behavioral impairment in either task (Sack, Sperling, et al. 2002).

Importantly, in the current study, we revealed that TMS to the right parietal cortex resulted not only in a relative decrease of neural activity within the vicinity of the stimulated right SPL but also in several frontal regions within the same hemisphere (Fig. 2). This TMS-induced reduction of neural activity within a specific right-hemispheric frontoparietal network was significantly stronger for the visuospatial judgment task (ANGLE) than for the visuocolor discrimination task (COLOR). Hence, the same task that showed the significant behavioral impairment also showed stronger neural effects of right parietal magnetic stimulation. Moreover, only the right SPL and MFG showed a significant correlation between the degree of reduced neural activity and the strength of the behavioral visuospatial impairment induced by TMS.

Several models have been proposed that attribute different functional roles to different regions within the posterior parietal cortex, especially SPL and IPL. Based on neuropsychological findings, Goodale and Milner (1992) described a dorsal "vision-for-action" system that is involved in computing target positions in an egocentric reference frame for the immediate control of reaching, grasping, or eye movements. A central part of the dorsal system is the SPL, lesions of which can produce severe deficits in visually guided movements (optic ataxia). The IPL does not easily fit into the scheme of Milner and Goodale, but it would most likely be considered part of the ventral "vision-for-perception" stream (Milner 1997). In a similar vein, Rizzolatti and Matelli (2003) consider the SPL to be part of a system involved in the online control of action, whereas the IPL is dedicated to action understanding and spatial perception. A third view on the division of labor in the parietal cortex emphasizes the different types of attentional processing that are subserved by SPL and IPL regions. Corbetta and Shulman (2002) argue that SPL and parts of the IPS are relevant for the top-down control of visual attention and the selection of appropriate responses. In contrast, the IPL and more specifically the temporoparietal junction are involved in redirecting attention in a stimulus-driven manner when salient events occur. These theories thus focus on 2 main functions for the SPL: visuomotor transformations and attentional control, whereas spatial perception of the stimulus is mainly related to IPL not SPL.

In contrast, Husain and Rorden (2003) and Husain and Nachev (2007) emphasize the role of the IPL in spatial processing and describe studies demonstrating nonspatial functions for the IPL. In addition, there is a large body of evidence relating areas in the SPL to visuospatial processing using PET (Haxby et al. 1991; Ungerleider and Haxby 1994; Mellet et al. 1996), fMRI (Cohen et al. 1996; Tagaris et al. 1996; Goebel et al. 1998; Carpenter et al. 1999; Trojano et al. 2000; Ng et al. 2001; Formisano et al. 2002; Trojano et al. 2002; Vannini et al. 2004; Schicke et al. 2006), and TMS (Sack, Hubl, et al. 2002; Sack, Sperling, et al. 2002; Blanke et al. 2003) to visuospatial tasks.
et al. 2005; Kim et al. 2005; Koch et al. 2005; Göbel et al. 2006). It is possible that the spatial functions represented in the right parietal network we find are also used for visuomotor transformations and attentional control. Nevertheless, we do not think that our results can be explained by nonspecific effects of attention because we used an adequate control task (COLOR) that used the same stimulus material and required attention to the same stimulus parts (clock pointers). In general, many different functions have been described for the parietal cortex, and until now it is unclear how many separate systems can be

Figure 4. Functional brain connectivity during task execution. (A) Group fMRI analyses of functional connectivity during the ANGLE task execution (upper part) versus COLOR task execution (lower part) without TMS using GCM. The right parietal reference ROI was defined based on the GLM contrast “task execution with versus without TMS.” Areas color coded in red represent brain areas that show functional connectivity during task execution. (B) The network of functional connectivity as revealed by GCM is superimposed on the GLM contrast “angle task execution with versus without right parietal TMS.” The GLM results are color coded in blue-orange, blue representing areas with a TMS-induced decrease of neural activity during ANGLE task execution. The GCM is color coded in red, representing the brain areas showing functional connectivity during the ANGLE task execution. Close-up windows are provided for the 3 overlapping ROIs: right SPL, right postcentral gyrus, and right MFG.
distinguished (Culham and Kanwisher 2001; Culham and Val- year 2006). Further experiments using different paradigms in the same subjects will be needed to determine the amount of overlap between the frontoparietal networks described in the literature and in our study.

Our study also revealed that right parietal TMS during central fixation, and thus without active visuospatial task performance, did not result in any frontoparietal activity reductions (Supple- mentary Fig. 3A), indicating that the neural effects of TMS are shaped by the task at hand. In other words, focal parietal TMS produced function-dependent network activation patterns that varied with task demands. This demonstrates the dependence of the neural effects of TMS on the physiological state of the stimulated brain area. Although during resting state no signifi- cant neural effect of TMS might be observed, such significant neural effects can still be unmasked during the execution of a task that requires activation of the targeted brain area. One might thus speculate that the revealed right-hemispheric frontoparietal network of reduced brain activity represents those brain areas that functionally contribute to successful visuospatial task performance. This notion is further supported by the fact that independently computed functional connectivity analyses identified the exact same brain areas as being functionally connected specifically during visuospatial task execution (Fig. 4). In this context, the concurrent combination of TMS and fMRI during active task execution might be a means to visualize task-specific brain networks of functional connect- ivity. Our data clearly suggest that the TMS-induced direct and indirect neural effects during task execution ride on the task- induced brain network activation as revealed by classical GLM and functional connectivity analyses. This means that the exact neural impact of TMS as revealed by fMRI might be the result of a complex interaction between the magnetic stimulation itself and the physiological state of the targeted brain area including its functionally connected brain regions. The physiological state of this brain network is in turn shaped by the execution of the respective behavioral function it attempts to subserve at the moment of the insult. Similar findings of TMS affecting func- tional and effective brain connectivity networks have been reported based on different methodological approaches. By measuring task-related brain activity before and after the magnetic stimulation using fMRI analyses of effective brain connectivity changes, Pleger et al. (2006) could demonstrate that repetitive transcranial magnetic stimulation over the primary somatosensory cortex (S1) results in a reconfiguration of neural activity in S1 and ipsilateral PMC (M1). This sensorimotor network reorganization included a TMS-induced increase in neural activity over the directly stimulated brain area (S1), as well as an increase in the effective connectivity from S1 to M1, both being correlated with behavioral improvements in a tactile discrimination task. Other studies also report behaviorally relevant effects of TMS on remote brain areas that are functionally connected to the focal TMS target site (Silvanto et al. 2005, 2006; Ruff et al. 2006; Taylor et al. 2007). Future studies simultaneously combining TMS and fMRI are advised to consider these task- and state-dependent neural effects of TMS when designing and interpreting their experiments.

The right-hemispheric lateralization of functionally relevant frontoparietal activity during visuospatial processing as revealed in our study parallels the models of classical neuropsychology that are based on findings of hemispatial neglect after unilateral parietal damage. Most of the neuropsychological literature points to a prominent role of the right parietal lobe in visuo- spatial functioning, especially the IPL (Vallar et al. 1996; Vallar 1997; Mesulam 1999; Driver and Vuilleumier 2001). For example, contralosional hemineglect in humans is almost always associated with right-hemispheric brain lesions whereas lesions to homologous brain areas in the left hemisphere rarely cause visuospatial deficits of comparable frequency or severity. These neuropsychological findings have been explained with an asymmetrical distribution of spatial attention (Mesulam 1999). However, although most neglect patients develop visuospatial deficits after a lesion of the right parietal brain region, similar symptoms have also been reported after brain damage to the right prefrontal cortex and after unilateral lesions of the superior colliculus and the pulvinar. In addition, TMS studies reporting neglect-like symptoms often use stimulation sites above the IPS and SPL, as in our study, and not above the IPL (Hilgetag et al. 2001; Müri et al. 2002); and also brain imaging studies have described asymmetric patterns of activity in the SPL for visuospatial attention (Corbetta et al. 1993). Therefore, it remains unclear whether the right-hemispheric effect we see in our data depends on neural substrates that are also affected during spatial hemineglect or whether a similar asymmetrical pattern has developed in parallel for separate systems in the SPL and IPL.

The novel approach of simultaneously combining fMRI, TMS, and behavioral studies, as realized in the current study, revealed first insights into the direct and remote neural activity changes underlying impaired visuospatial processing during parietal TMS. Our results enabled us to directly relate the asymmetry of behavioral consequences following left versus right parietal lesions, as revealed in both neuropsychological lesion and TMS studies, to an asymmetry of the respective neural effects in the active human brain. Whereas right parietal TMS resulted in a task-specific neural activity reduction along a right lateralized frontoparietal network that covaried with impaired visuospatial judgments, left parietal TMS led to no task-specific activity decreases (Fig. 3). The absence of behavioral effects following left parietal TMS is thus mirrored by an absence of TMS-induced reductions of neural activity. Accordingly, no interaction between TMS and TASK condition and no correlations between TMS-induced activity changes and task performance were found during left parietal TMS. The absence of significant activity changes at the site of stimulation in left parietal cortex might seem puzzling at first, considering that the parietal lobes of both hemispheres showed activity increases during execution of both tasks and considering that the functional connectivity analyses also revealed a bilateral frontoparietal network during visuospatial judgments. However, a direct comparison of neural activity during the ANGLE versus COLOR task execution revealed significantly more activity in right parietal cortex during the ANGLE task (Supplementary Fig. 2A). This stronger right parietal activity during the visuospatial judgment task may have facilitated the effect of TMS. This would be analogous to the observation that TMS to PMC induced stronger peripheral muscle movements and facilitated motor-evoked potentials when applied during voluntary contraction as opposed to a relaxed muscle state (Tunstill et al. 2001).

There are several possible explanations for our results in distant brain areas. The most straightforward explanation would be that the local neural effects of TMS propagate to intercon- nected brain regions. Several studies show that this can indeed be the case (Ferbert et al. 1992; Givardi et al. 2001; Daskalakis et al. 2005). Further experiments using different paradigms in the same subjects will be needed to determine the amount of overlap between the frontoparietal networks described in the literature and in our study.
et al. 2004). For example, recent neuroimaging studies showed activity changes correlated to TMS in broad functional networks within the brain (Chouinard et al. 2003; Speer et al. 2003a, 2003b; Li et al. 2004), including basal ganglia (Strafella et al. 2001) and the thalamus (Bestmann et al. 2004; Denoslow et al. 2005). Moreover, neural network models indicate that the effects of TMS propagate to both directly and indirectly connected remote sites (Husain et al. 2002). Yet, a prerequisite for such an explanation is the existence of respective anatomical connections between the stimulated SPL and the identified remote brain regions within lateral frontal cortex. Anatomical tracing studies in macaques (Petrides and Pandya 2006) have indeed shown that areas 8Ad, 8Av, and 8B, which are parts of the caudal prefrontal region, are connected with areas in the intraparietal sulcus (areas IPd and POa) via the superior longitudinal fasciculus (SLF II) and the frontoocipital fasciculus. Another component of the SLF, the SLF I fibers, connects midlateral prefrontal areas 9/46d and 9/46w with areas PGm, PEC, and PEci. (PE is equivalent to human SPL, see Parvizi et al. 2006). Furthermore, fibers of SLF II connect areas 9/46 to area PG (IPL).

In the present study, the revealed remote activity changes in the right frontal cortex were functionally coupled with activity at the parietal site of stimulation during the execution of the task in question, and activity changes both at the site of stimulation and remote brain regions may have therefore caused the behavioral perturbation we observed. Alternatively, the observed remote activity changes may be a consequence of the perturbed behavior. It is conceivable that TMS mainly exerts its behavioral effect by disrupting activity at the site of stimulation, but activity in additional remote brain regions reacts to this disruption, exhibiting activity changes that are highly correlated to the site of stimulation. We also cannot exclude the possibility that the remote activity changes simply covaried with local and presumably causally relevant activity changes but did not contribute to the behavioral perturbation.

Although the exact physiological underpinnings of TMS-induced activity decreases require more detailed future investigation, our study exemplifies how concurrent TMS and fMRI can be used to chart brain activity changes to a transient TMS-induced behavioral perturbation noninvasively and with high spatial precision. In particular, we have confirmed the involvement of right parietal cortex in visuospatial processing and shown that a TMS-induced impairment of this behavior is paralleled not only by activity changes at the site of disruption but also by ipsilateral activity changes in lateral frontal cortex.

Conclusions

We propose that the simultaneous combination of TMS with fMRI during active task execution provides an important opportunity to assess the direct and remote neural underpinnings of virtual brain lesions. In this sense, concurrent TMS and functional imaging should be regarded as a complementary approach to behavioral TMS studies, helping to refine the causal topography of structure-function relationships across the entire brain. The challenge for future studies will be to disclose the functional relevance of the TMS-induced direct and remote neural effects, aiming to distinguish brain areas that cause the behavioral changes from those that simply represent covariates or consequences of the induced changes in cognition and behavior.

Supplementary Material

Supplementary material can be found at http://www.cercor. oxfordjournals.org/.

Notes

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