

Tracking the mind's image in the brain II: Differential effects of repetitive transcranial magnetic stimulation of the right and left parietal lobe.

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Tracking the Mind's Image in the Brain II: Transcranial Magnetic Stimulation Reveals Parietal Asymmetry in Visuospatial Imagery

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Summary

The functional relevance of brain activity during visuospatial tasks was investigated by combining functional magnetic resonance imaging with unilateral repetitive transcranial magnetic stimulation (rTMS). The cognitive tasks involved visuospatial operations on visually presented and mentally imagined material (“mental clock task”). While visuospatial operations were associated with activation of the intraparietal sulcus region bilaterally, only the group which received rTMS to the right parietal lobe showed an impairment of performance during and immediately after rTMS. This functional parietal asymmetry might indicate a capacity of the right parietal lobe to compensate for a temporary suppression of the left. This is compatible with current theories of spatial hemineglect and constitutes a constraint for models of distributed information processing in the parietal lobes.

Introduction

Functional neuroimaging techniques like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been used extensively to

study the cerebral mechanisms of visuospatial processing. Partially overlapping fronto-parietal networks have been identified for visual attention and eye movements (Corbetta et al., 1998), visuospatial transformations (Goebel et al., 1998; Carpenter et al., 1999), visual search (Leonards et al., 2000), and spatial memory (Diwadkar et al., 2000). Parametric variation of the demand on specific visuospatial functions revealed a differential modulation of the intraparietal sulcus (IPS) regions bilaterally in response to increased difficulty of visuospatial transformations (Carpenter et al., 1999) and a separation of the visuospatial transformation and oculomotor systems in the parietal lobes (Goebel et al., 1998). Frontoparietal networks also seem to be involved in visuospatial imagery (Trojano et al., 2000; Lamm et al., 2001; Mellet et al., 1996) while the extent of the involvement of occipital areas is still a matter of debate (Klein et al., 2000; Mellet et al., 1998, 2000; Roland and Gulyás, 1994; Kosslyn and Ochsner, 1994). The bilateral IPS regions were found to be activated in visual imagery when spatial comparison between imagined objects had to be performed in the mental clock task (Trojano et al., 2000, 2002). These activated areas in the posterior parietal lobe showed a high overlap between visual matching of perceived and imagined clocks, which was interpreted as evidence for a common neural basis for the analysis of visual space in perception and imagery (Trojano et al., 2000). A single-trial fMRI study of the mental clock task revealed different components of the fronto-parietal network, according to their place in the temporal sequence of activation (Formisano et al., 2002 [this issue of *Neuron*]).

It has been claimed recently, on the basis of a large lesion study, that spatial awareness is represented in the right superior temporal rather than the parietal cortex (Karnath et al., 2001). There is considerable difficulty in reconciling this observation with most of the functional neuroimaging literature. Yet, lesion studies that are based exclusively on structural imaging data have to be interpreted with caution because of the effects of functional reorganization (Jenkins et al., 1990) or the functional impairment of remote areas (diaschisis) (Seitz et al., 1999).

In this study, we aimed to overcome this difficulty by combining evidence from transient functional lesions induced by repetitive transcranial magnetic stimulation (rTMS) with that from functional imaging in order to address the question of the functional relevance of parietal activation during visuospatial processing (Sack et al., 2002) and mental imagery (Kosslyn et al., 1999). By inducing transient regional deactivations, rTMS provides a possibility to manipulate brain activity as an *independent variable* and to investigate its influence on the performance of different cognitive tasks within a controlled experimental design (Hallett, 2000). Compared to studies that combine functional imaging with neuropsychological deficits occurring in structural brain damage, the functional deficits induced by TMS are far more transient, and therefore its effect is unlikely to bring about functional reorganization or the functional impairment of remote areas (Walsh and Rushworth, 1999). The meth-

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odological approach of our study thus enabled us to investigate the causal relationship between unilateral parietal activation and the execution of visuospatial tasks, based on physically presented as well as mentally imaged stimuli, and presents a systematic experimental investigation of potential functional hemispheric asymmetry of parietal activation for perceptual visuospatial processing and visuospatial imagery.

The conjoint use of fMRI and TMS was a critical aspect of our study because it lends a face validity to the interpretation of the TMS results. In particular, we were able to show that the sites of TMS stimulation, inducing transient lesions, were over cortical regions that responded selectively to the tasks under investigation. We were able to do this by the use of fiducial markers that linked the TMS sites and regional activations in fMRI.

We investigated spatial operations on visually presented as well as mentally imaged stimuli. In the angle and color discrimination task, we presented a series of analog clocks, each shown for 400 ms with an interstimulus-interval (ISI) of 900 ms. The color of the hands and the angle between the hands varied between the stimuli. Subjects had to press a button whenever a target stimulus appeared. Targets were defined as clocks with angles of 60° or 30° (angle discrimination task) or clocks with white hands (color discrimination task). In the mental clock task subjects were asked to imagine two analog clock faces based on acoustically presented times, and to judge at which of the two times the clock hands form the greater angle. Subjects were asked to press the left mouse button if the hands of the first clock formed the greater angle, or the right mouse button for the second. Subjects' responses were registered by an optic fiber answer box and analyzed for reaction time and accuracy.

For the fMRI study, six healthy subjects were recruited. The two visually presented tasks (angle + color discrimination) were performed in one session following the classical block design. The mental clock task was performed in one session on the basis of an event-related design. Vitamin E capsules were used to mark the positions P3 and P4 of the international 10–20 EEG system on the scalp of each subject for coregistration with TMS. P3 and P4 represent standardized points within the EEG grid system corresponding to the posterior parietal cortices (Homan et al., 1987). MRI data were acquired with a 1.5 T MAGNETOM Vision MRI scanner (Siemens Medical Systems, Erlangen, Germany) using the standard head coil.

fMRI data analysis and visualization were performed using the BrainVoyager 4.4 software package. The statistical analysis of the variance of the BOLD signal in the visual paradigm was based on the application of multiple regression analysis to time series of task-related functional activation (Friston et al., 1995). For significantly activated voxels, the relative contribution *RC* between two selected sets of conditions in explaining the variance of a voxel time course was computed. An *RC* value of 1 (red) indicates that a voxel time course is solely explained with predictor 1 whereas an *RC* value of -1 (blue) indicates that a voxel time course is explained solely with predictor 2 (Trojano et al., 2000). The statistical analysis of the temporal sequence of BOLD signal changes during the mental paradigm was

based on a relative latency map (see Formisano et al., 2002).

In the rTMS experiment, 60 subjects were randomly assigned into three groups (stimulation for 12 min at 1 Hz and 110% of motor threshold (MT) over the parietal electrode positions P3 and P4, and sham condition (see Experimental Procedures)). A custom TMS stimulator (MagPro, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) was used to generate repetitive biphasic magnetic pulses. Magnetic pulses were delivered with a figure-eight-coil (Magnetic Coil Transducer MC-B70, Medtronic). Performance was measured at four different times: as a pretest, during TMS (stimulation), immediately after TMS (posttest 1), and 12 min after TMS (posttest 2). In order to control for possible effects of rTMS on motor response, we included a finger tapping task for both hands at all four times of measurement. The used rTMS protocol has been shown to suppress transiently cortical excitability during as well as for several minutes beyond the rTMS stimulation period (Chen et al., 1997; Kosslyn et al., 1999; Sack et al., 2002; Pascual-Leone and Hallett, 1994).

Results

fMRI Experiment

Both conditions of the visual paradigm, angle and color discrimination, were accompanied by a significant increase in the BOLD signal in primary visual cortex compared to baseline. The color condition, compared to baseline, additionally activated the right superior occipital gyrus and the lingual gyrus. The angle condition showed several additional significant clusters of activation, both compared to baseline and compared to the color discrimination condition within a statistical *RC* map, in the left and right superior parietal lobule (SPL), the precuneus, and the right middle frontal gyrus (Table 1). A contrast analysis revealed that the BOLD signal changes in the areas with an *RC* index in favor of the angle discrimination task were significantly different between the angle and color discrimination condition. The low frequency of motor responses in both conditions explains the lack of motor cortex activity.

The significantly activated areas in the parietal lobes that were exclusively explained by the angle discrimination task were located directly below the vitamin E capsules, marking electrode positions P3 and P4 and corresponding to the anatomical area of the superior IPS, bilaterally (Figure 1).

The event-related design used in the mental clock task enabled us to measure the temporal sequence of activation occurring between the acoustical onset and button press. Since half of the subjects were asked to respond with their left hand, we divided the sample into subjects with left button press and right button press. We found significant activation that corresponded to the temporal sequence of mental processes during the execution of the mental clock task, starting with activity in left and right Heschl's gyrus, followed by supplementary motor area (SMA), frontal eye fields (FEF), precuneus, left and right posterior parietal cortex (PPC), and finally primary motor cortex (PMC) of the side contralateral to the hand used for button press (Tables 2 and 3).

Table 1. Talairach Coordinates (plus BA's) for Activated Clusters during the Visual Clock Paradigm

Anatomical Area	BA	Angle versus Color			Angle versus Baseline			Color versus Baseline		
		X	Y	Z	X	Y	Z	X	Y	Z
Right superior parietal lobule	7	29	-70	41	21	-69	49	-	-	-
Right superior parietal lobule	7	14	-76	48	16	-72	48	-	-	-
Left superior parietal lobule	7	-15	-69	52	-13	-67	52	-	-	-
Precuneus	7	-8	-68	53	-1	-72	49	-	-	-
Right middle frontal gyrus	46	35	39	27	36	35	28	-	-	-
Primary visual cortex	17	-	-	-	1	-75	7	2	-77	7
Gyrus lingualis	19	-	-	-	-	-	-	19	-57	-3
Right superior occipital gyrus	19	-	-	-	-	-	-	26	-73	27

The table shows the results of the computed angle versus color relative contribution (left part), angle versus baseline (middle part), and color versus baseline (right part) map.

Talairach coordinates of centers of mass of activated clusters $>400 \text{ mm}^3$ at $R > 0.40$ for (a) angle versus color relative contribution ($F = 28$ (12, 1403), $p < 0.01$ (corr.); RC index = 0.7), (b) angle versus baseline ($F = 44, 73$ (6, 1403); $p < 0.01$ (corr.)), and (c) color versus baseline ($F = 44.73$ (6, 1403); $p < 0.01$ (corr.)). BA = Brodmann Area.

The parietal clusters of activation in this imaginary visuospatial task were located below the vitamin E capsules, marking P3 and P4, corresponding to the anatomical areas of left and right superior IPS (Figure 2, Tables 2 and 3).

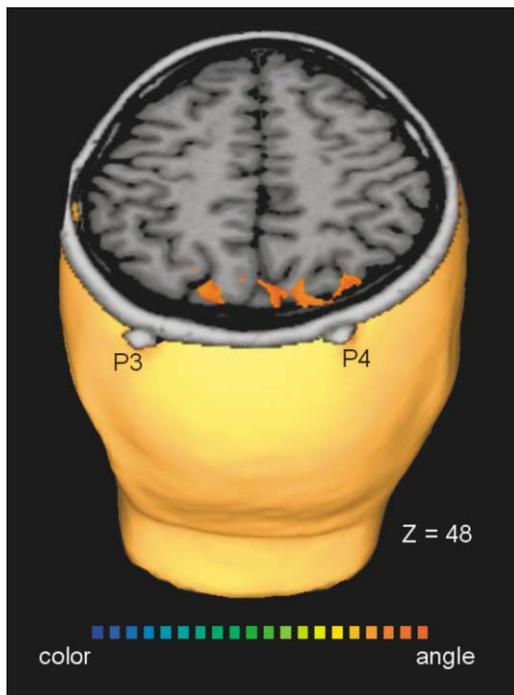


Figure 1. Cortex-Based Multiple Regression Analysis of the fMRI Time Series in the Visual Paradigm

Group analysis (GLM) of the visual paradigm for all subjects at $F = 28$ (12, 1403), $p < 0.01$ (corr.); RC index = 0.7). Color coded group statistical RC maps of BOLD signal increase for angle versus color discrimination superimposed on an axial cut of the anatomical data set of a single subject that shows the position of the capsules over P3 and P4. Blue color indicates that a voxel time course is explained mainly with the first predictor (color discrimination); red colors indicate that a voxel time course is explained mainly with the second predictor (angle discrimination task). The BOLD signal changes in these activated areas differed significantly between the angle and the color discrimination conditions ($t > 6$; corr. $p < 0.01$). Only RC values greater than 0.7 are visualized.

rTMS Experiment

The sham group showed a monotonic decrease in mean reaction time from pretest to posttest 2 in all of the three tasks, probably due to a familiarization effect. The two (real) stimulation groups showed a different pattern of change in mean reaction time between the times of measurement in the three tasks (Table 4).

The group that was stimulated over P3 (stim P3) showed a monotonic decrease in reaction time from pretest to posttest 2 in the angle discrimination and the mental clock tasks, and an almost unchanged reaction time in the color discrimination task. The group that was stimulated over P4 (stim P4) showed an increase in reaction time during stimulation and posttest 1 in the visual angle discrimination task. This increased reaction time decreased again in posttest 2. In the imagery discrimination task, the stim P4 group showed a slight increase in reaction time during stimulation and posttest 2. The change in mean reaction time in the color discrimination task was comparable to the stim P3 group (Table 4).

These results suggest that a difference between real and sham TMS in the performance of the visuospatial tasks, as expected on the basis of the hypotheses, only occurred in the stim P4 group, while the stim P3 group showed no noticeable differences from the sham group.

The one-way ANOVA for the visual angle discrimination task revealed a significant difference in mean reaction time between the groups for the stimulation (F [2, 57] = 7.582; $p = 0.001$) and in posttest 1 (F [2, 57] = 4.957; $p = 0.01$), but not for the pretest (F [2, 57] = 1.613; $p = 0.208$) or posttest 2 (F [2, 57] = 1.029; $p = 0.364$). The Scheffé procedure for multiple contrasts revealed that this significant main effect was attributable to a significant difference only between the stim P4 group and the sham group during stimulation and in posttest 1, while the stim P3 group showed no significant difference in comparison to the sham group at any of the times of measurement (Figure 3A). A direct comparison between the stim P3 and stim P4 group also revealed a significant difference during stimulation.

In the color discrimination task, no significant differences between the groups were found at any of the times of measurement (Figure 3B).

The one-way ANOVA for the mental clock task showed

Table 2. Talairach Coordinates (plus BA's) for Activated Clusters during the Mental Clock Paradigm

Anatomical Area	F Value	BA	Stimulus Onset versus Button Press			Interindividual Variance			Cluster Size Voxel
			X	Y	Z	X	Y	Z	
Right Heschl's gyrus	410	41	+50	-19	+9	- ±3	±3	±5	8,084
Left Heschl's gyrus	386	41	-52	-24	+11	- ±2	±5	±2	9,741
Gyrus frontalis medialis (SMA)	117	6	±0	±0	+51	- ±0	±7	±3	2,765
Left precentral gyrus (FEF)	162	6	-45	-6	+42	- ±2	±8	±8	2,959
Left middle frontal gyrus	90	9	-47	+18	+35	- ±4	±5	±1	729
Left superior occipital gyrus/ Left superior parietal lobule	82	19/7	-29	-80	+31	- ±6	±8	±3	226
Left superior parietal lobule	76	7	-19	75	48	- ±9	±3	±2	1,075
Right superior parietal lobule	42	7	+34	-71	+35	- ±6	±4	±6	217
Right superior parietal lobule	34	7	25	-71	50	- ±8	±2	±5	800
Right middle frontal gyrus	85	9	+47	+18	+38	- ±6	±1	±4	676
Left postcentral gyrus	213	2	-46	-35	+51	- ±2	±14	±5	10,096
Precuneus	85	7	±0	-77	+42	- ±8	±1	±1	427

The table shows the results of the relative latency map (left part) for subjects with right hand button press (multi-study GLM), the interindividual variance in Talairach coordinates and the number of activated voxels from the group map.

Talairach coordinates of centers of mass of activated clusters > 100 mm³ at R > 0.22 for (a) relative latency map (F = 30 (2, 1183), p < 0.01 (corr.)), (b) interindividual variance in Talairach coordinates of these clusters, (c) number of activated voxels. BA = Brodmann Area.

a significant difference in mean reaction time between the groups during stimulation (F [2, 57] = 3.476; p = 0.038) and in posttest 2 (F [2, 57] = 6.940; p = 0.002). As the Scheffé procedure reveals, this significant group main effect was again due to significant differences only between the stim P4 group and the sham group, and between the stim P4 group and the stim P3 group, while the stim P3 group showed no significant difference in comparison to the sham group at any of the times of measurements (Figure 3C).

After including the time of measurement as a separate factor in the statistical analysis, we computed a two-way ANOVA for repeated measurements testing for possible

interactions between the group factor and the time of measurement. The two-way ANOVA for the visual angle condition revealed a significant interaction between the group factor and the time of measurement only for the comparison between stim P4 and the sham group (F [3, 57] = 8.827; p = 0.00), while the stim P3 group showed no significant difference in its change between the time of measurement in comparison to the sham group (F [3, 57] = 0.231; p = 0.874).

For the visual color discrimination task, no significant interactions between either of the groups and the times of measurement were found.

In the mental clock task, a significant interaction be-

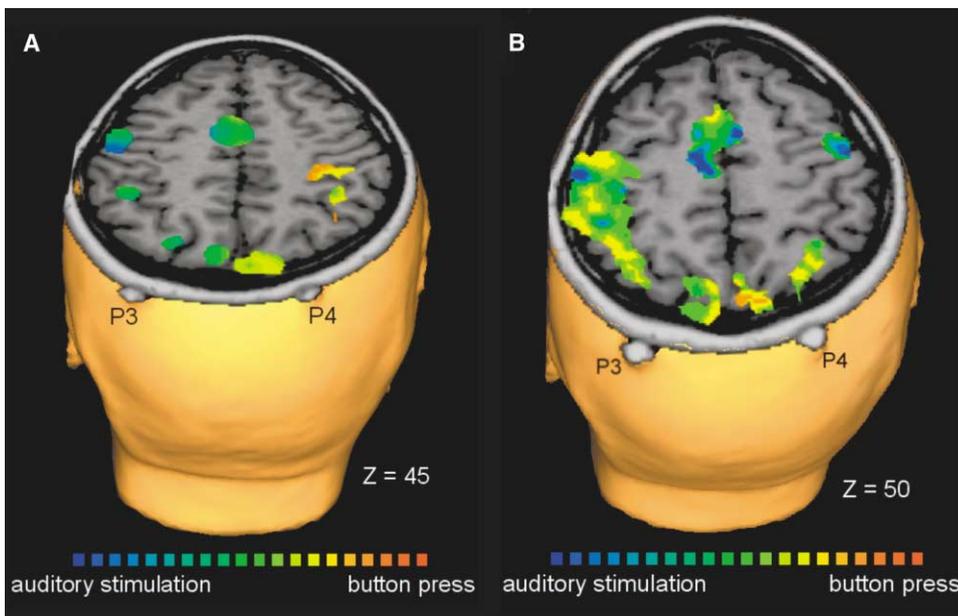


Figure 2. Cortex-Based Multiple Regression Analysis of the fMRI Time Series in the Mental Paradigm

Group relative latency map (GLM) of the mental paradigm for (A) subjects with left hand response at F = 80 (2, 1183), p < 0.01 (corr.) and for (B) subjects with right hand response at F = 30 (2, 1183), p < 0.01 (corr.). The relative latency maps are superimposed on axial cuts of the anatomical data set of a single subject showing the capsules positioned over P3 and P4. The color code denotes the onset latency of BOLD activation in relation to the auditory presentation of the stimulus.

Table 3. Talairach Coordinates (plus BA's) for Activated Clusters during the Mental Clock Paradigm

Anatomical Area	F Value	BA	Stimulus Onset versus Button Press			Interindividual Variance			Cluster Size
			X	Y	Z	X	Y	Z	Voxel
Right Heschl's gyrus	305	41	58	-9	11	- ±7	±8	±3	597
Left Heschl's gyrus	278	41	-56	-33	15	- ±1	±2	±3	1127
Left precentral gyrus (FEF)	300	6	-47	0	34	- ±4	±3	±5	4298
Left precuneus	153	7	-9	-72	48	- ±4	±8	±4	517
Left superior parietal lobule	114	7	-25	-66	43	- ±8	±6	±3	239
Gyrus frontalis medialis (SMA)	264	6	-3	0	44	- ±1	±3	±5	3239
Left inferior parietal lobule	230	7	-43	-44	54	- ±6	±3	±5	1630
Right precuneus	161	7	8	-78	46	- ±2	±4	±2	1045
Left precentral sulcus	215	4	-30	-10	59	- ±6	±23	±9	1903
Right precentral gyrus	199	4	34	-29	56	- ±0	±8	±8	2188
Right superior parietal lobule	146	7	35	-54	54	- ±7	±6	±11	590

The table shows the results of the relative latency map (left part) for subjects with left hand button press (multi-study GLM), the interindividual variance in Talairach coordinates, and the number of activated voxels from the group map.

Talairach coordinates of centers of mass of activated clusters > 200 mm³ at R > 0.34 for (a) relative latency map (F = 80 (2, 1183), p < 0.01 (corr.)), (b) interindividual variance in Talairach coordinates of these clusters, (c) number of activated voxels. BA = Brodmann Area.

tween the group factor and the time of measurement was found only in the comparison between the stim P4 and the sham group (F [3, 57] = 3.931; p = 0.01), while no significant interactions between the group and time of measurement factor were found when comparing the sham group with the stim P3 group (F [3, 57] = 1.846; p = 0.143).

No significant group differences for the left or the right finger tapping task were found at any of the times of measurement.

Since the three groups were not statistically matched for gender or handedness, both variables were separately included as independent factors within a three-way ANOVA in order to test for possible second-order interactions between gender, group, and time of measurement or handedness, group, and time of measurement. No significant second order interactions for any of the tasks were found.

Discussion

There is convincing evidence for the activation of a fronto-parietal network during spatial and nonspatial at-

tention tasks (Wojciulik and Kanwisher, 1999). Although heterogeneous stimuli and tasks produce parietal activation (Culham and Kanwisher, 2001), a large body of neuropsychological literature points to a particular role for the PPC in visuospatial functioning. Evidence from lesion studies seems to confirm the neurophysiological finding of multiple space representations in the PPC (Colby and Goldberg, 1999; Landis, 2000; Marshall and Fink, 2001).

The fMRI results on the visually presented tasks largely confirmed findings from our group's previous studies on the same paradigm. The most prominent differences in cortical activation during the detection of angles compared to that of variations of color were found in the superior IPS bilaterally (Sack et al., 2002). Moreover our finding that only suppression of the right IPS region by rTMS led to behavioral effects on spatial tasks in visual perception during and immediately after (posttest 1) TMS is in accordance with most of the neuropsychological literature, which points to a prominent role for the right parietal lobe in visuospatial functioning (Vallar et al., 1996; Mesulam, 1999; Driver and Vuilleumier, 2001) and suggests that our previous finding of

Table 4. Mean Reaction Times of the Three Groups in the Three Tasks in ms plus Standard Deviation

Mean Reaction Time in ms (SD) of the Visual Angle Task					
	N	Pretest	Stimulation	Posttest 1	Posttest 2
Stimulation group P4	20	436.662 (34.804)	464.485 (19.338)	460.318 (20.613)	436.974 (39.447)
Stimulation group P3	20	455.351 (34.929)	440.766 (34.668)	441.516 (33.414)	439.674 (34.575)
Sham group	20	441.285 (33.068)	429.197 (31.382)	431.430 (32.568)	424.553 (32.278)
Mean Reaction Time in ms (SD) of the Visual Color Task					
	N	Pretest	Stimulation	Posttest 1	Posttest 2
Stimulation group P4	20	361.553 (33.204)	367.542 (39.706)	368.605 (41.228)	367.983 (37.083)
Stimulation group P3	20	356.536 (35.969)	361.553 (33.204)	361.143 (33.764)	354.723 (36.627)
Sham group	20	348.615 (27.622)	347.181 (31.953)	346.369 (33.966)	343.880 (24.596)
Mean Reaction Time in ms (SD) of the Mental Clock Task					
	N	Pretest	Stimulation	Posttest 1	Posttest 2
Stimulation group P4	20	5.197 (0.630)	5.230 (0.666)	5.026 (0.570)	5.285 (0.913)
Stimulation group P3	20	5.046 (0.556)	4.816 (0.494)	4.862 (0.476)	4.723 (0.432)
Sham group	20	5.142 (0.457)	4.890 (0.391)	4.775 (0.364)	4.615 (0.314)

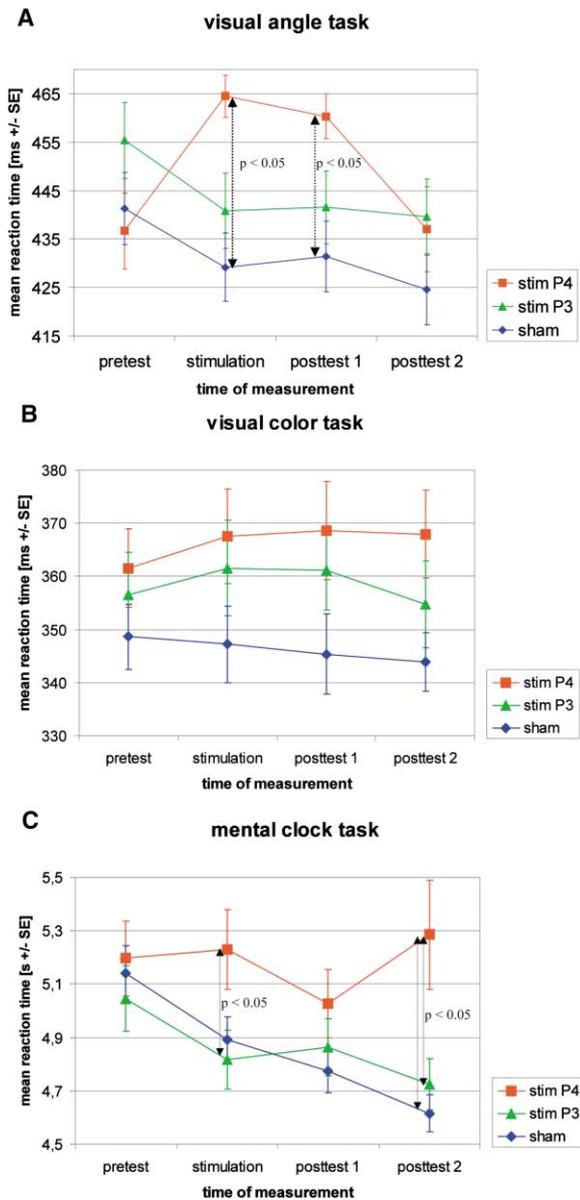


Figure 3. Influence of Unilateral rTMS on Mean Reaction Times in the Tasks

Mean reaction times in the (A) angle discrimination task, (B) color discrimination task, and (C) mental clock task at the four times of measurement (pretest, stimulation, posttest 1 and 2) for the three groups.

impaired performance of the angle discrimination task after rTMS over the parietal midline (Sack et al., 2002) could be attributed to the part of the induced magnetic field that affected the right hemisphere. While that study has merely shown a disruption of the normal learning effect, we now can show a significant impairment of task performance during and after rTMS. This stronger effect is probably brought about by the increased specificity of the unilateral stimulation. Additionally, this stronger effect can be interpreted as a consequence of the higher TMS intensity used in this study (110% MT) in comparison to the previous study (80% MT), confirm-

ing the evidence of combined fMRI/rTMS studies revealing an intensity-dependent effect of rTMS on induced local brain activity (Bohning et al., 1999).

In the field of visual imagery, the neuropsychological evidence parallels that from functional imaging studies in that similar mechanisms seem to govern the spatial analysis of imagined and perceived objects (Farah, 1989; Trojano and Grossi, 1994). Several neuropsychological and imaging studies proposed a dominant role of the left hemisphere in imagery (Farah et al., 1985; D'Esposito et al., 1997). However, the fMRI experiments reported in this and the companion paper (Formisano et al.) demonstrate a bilateral parietal activation during the execution of visuospatial imagery and suggest that visuospatial imagery is associated with a more distributed activation than previously thought.

In PPC, Formisano et al. distinguish a cluster that is activated early during the task and shows a bilateral distribution (but left predominance) from a late cluster that is confined to the right PPC. The *duration* of activation of the early cluster and the *onset* of the (late) right cluster correlates with reaction time. It is suggested that the early and late clusters support different components of the cognitive process; for example, the generation and subsequent analysis of the visual image. These findings are in accordance with several studies proposing a model of bilateral activation in visuospatial imagery. These modular models suggest that the generation of mental imagery from memory relies primarily on structures in the posterior left hemisphere, while visuospatial operations on these images rely primarily on structures in the posterior right hemisphere (Farah, 1989). Our fMRI results of bilateral parietal activation during visuospatial imagery could therefore be interpreted as supporting such a modular model of visuospatial imagery.

Nonetheless, while fMRI alone can provide the temporal sequence of activation during the mental clock task, it reveals little about the functional relevance of this activation and about compensatory mechanisms. In our study, we were able to address this by using unilateral rTMS to disrupt transiently the activation of either hemisphere and study the respective effect of this unilateral functional lesion on task performance.

The coregistration of the stimulation sites (P3 and P4) with the MR images through vitamin E capsules revealed that TMS was applied over the parietal areas most strongly involved in the mental clock task (Tables 2 and 3).

The effect of rTMS on task performance revealed a hemisphere-specific effect of parietal stimulation. While there was no significant difference between the sham and the left stimulation (P3) group, subjects who were stimulated over the right parietal lobe (P4) performed significantly worse (measured by reaction time) than the other groups during and after rTMS.

Our results thus contribute significant constraints to the modular model of bilateral activation in visuospatial imagery by revealing a bilateral parietal activation during the execution of visuospatial tasks, both based on physically presented as well as mentally imagined stimuli, but a hemispheric asymmetry in the functional relevance for the performance of these tasks with the right PPC being able to compensate for suppression of the left PPC, but not vice versa (Trojano and Grossi, 1994; D'Es-

posito et al., 1997). One of these constraints affects the claimed lateralization of different aspects of the visuospatial imagery process. If left hemispheric activation underlies image generation and right hemispheric activation reflects the visuospatial operations on these images, a suppression of either of these clusters would lead to impaired task performance. If some components of the cognitive task are supported by a spatially more distributed network than others, they will suffer less disruption from focal functional lesions. In the case of the present study, the later (exclusively right parietal) cluster is fully affected by rTMS over right PPC while the earlier (and more distributed) cluster is not completely disrupted by the corresponding treatment of the left PPC. The transient functional lesion of the right PPC might thus have affected a highly localized functional cluster while the transient functional lesion of the left PPC could be compensated for by other parts of the network.

Such an explanation would be compatible with the current experimental evidence and theories on spatial hemineglect. Contralesional hemineglect in humans is almost always associated with right hemispheric lesions. This neuropsychological finding has been explained with an asymmetrical distribution of spatial attention (Mesulam, 1999), according to which the left hemisphere shifts attention in a contraversive direction while the right hemisphere directs attention in both directions (thus participating in a bilateral attentional network for the right hemisphere). In this model, a lesion of the right hemispheric attention network would lead to hemineglect for the left hemisphere (which is not within the attentional focus of the left hemisphere), whereas a corresponding left hemispheric lesion could be compensated for by the preserved (right) hemisphere which also covers the contralesional (right) hemisphere. Regardless of the general compatibility of this interpretation with the experimental evidence on spatial hemineglect, our results are not fully consistent with the neglect literature. While most imaging studies reveal PPC activity during the execution of spatial tasks and although neglect has traditionally been associated with parietal lesions, Karnath et al. (2001) recently reported on the basis of a large lesion study that awareness of the contralateral space is represented in the right superior temporal rather than the parietal lobe.

Nonetheless, the consideration of spatial hemineglect reveals important parallels to the present study. In both cases, the right hemisphere is capable of compensating for a disruption of the left hemispheric network for visuospatial processing. This suggests that while the cortical representation of some visuospatial functions might be highly lateralized to the right hemisphere, other important functions have a bilateral distribution, which allows the right hemisphere to compensate for lesions of visuospatial regions in the left hemisphere, but not vice versa. The combination of evidence from event-related fMRI and unilateral functional lesions induced by rTMS in the presented series of studies thus contributes new constraints to modular models of bilateral activation in visuospatial processing and imagery.

Our results furthermore reveal that the purpose of posttest 2 in the experimental design, originally included to reflect the temporal aspect of the TMS-induced effect

by a within-group comparison, was chosen within a time window not capable of representing such a temporal sequence, at least for the imagery task. Subjects showed a normal learning pattern during and after sham and left stimulation, but performed significantly worse during and after rTMS to the right PPC. Unlike the effect on the visual angle task, which returned to baseline in the second posttest (12–22 min after the end of the TMS train), the effect on the mental clock task became even stronger in the second posttest. In order to ensure that we did not induce any long-term effects on the performance in the mental clock task, we post hoc identified those subjects of the stim P4 group who showed a significant impairment in posttest 2 and retested their performance in all tasks several weeks after the experiment. All subjects had returned to their respective baseline performance. However, the precise temporal aspect of the TMS-induced effect on the mental clock task performance in these subjects remains speculative. The duration of reduced excitability of cortical areas stimulated with the rTMS protocol applied in this study has been estimated between 5 and more than 15 min (Hilgetag et al., 2001). Our finding of behavioral effects that lasted beyond 15 min and became even stronger with time emphasizes the importance of longer observation windows in future rTMS studies. Evidence from physiological studies suggests that rTMS might affect the efficiency of synaptic transmission and thus lead to a cortical suppression of the stimulated area that lasts for hours (Wang et al., 1996). Future studies should thus be designed to measure task performance over a broader time window, providing a quantitative estimate of the durations of the TMS effects on different perceptual and cognitive tasks.

Based on the presented temporal sequence of activation related to visuospatial imagery from left to right parietal cortex and the revealed hemispheric asymmetry for the execution of visuospatial tasks, a measurement of the temporal aspects of the processing of visuospatial information in the parietal cortex by time-triggered, single-pulse TMS can in the future lead to further and temporally more precise insights into the mechanisms of serial visuospatial information processing in the parietal lobes.

Experimental Procedures

Tasks

The cognitive tasks used in both the fMRI and rTMS experiments included a visual perceptual and an imagery paradigm.

In the visual paradigm, the stimuli consisted of visually presented analog clocks with a yellow face and two white or yellow hands on a black background. The angle between the hands varied in steps of 30° and the color of the hands was either white or yellow. Subjects had to press a button whenever a target stimulus appeared whereas targets were either defined as clocks with angles of 60° or 30° (angle discrimination task), or as clocks with white hands (color discrimination task). Stimuli were shown for 400 ms with an interstimulus interval of 900 ms. Stimuli were generated using the STIM software package (Neuroscan Inc. Herson, USA). Note that only the target-defining cue (angle versus color task) varied between conditions, while the stimuli were physically identical.

In the imagery paradigm, subjects were asked to imagine two analog clock faces based on acoustically presented times (e.g., 9.30 and 10.00), and to judge at which of the two times the clock hands form the greater angle (mental clock task). Subjects were asked to

press the left mouse button if the hands of the first imagined clock formed the greater angle, or the right mouse button for the second. Stimuli involved only half hours or hours and were balanced for the spatial side of the clock the hands had to be imagined on as well as the numerical value of the corresponding digital time. Subjects' responses were registered by an optic fiber answer box and analyzed for reaction times and accuracy.

Both experiments (fMRI and rTMS) were conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. All subjects gave their informed consent to participate in the respective study and reported being in good health and free of any psycho-active medication. There had been no incident of prior neurological disorder, including seizures, in any of the subjects.

fMRI Experiment

Subjects

Six healthy subjects were recruited (mean age 27.8 years, SD = 5.7). Subjects were balanced for gender (3 males, 3 females). All subjects were right handed. Half of the subjects were asked to use their left hand for the button response. Volunteers were naive within the limits of informed consent.

Apparatus and Procedure

MRI data were acquired with a 1.5 T MAGNETOM Vision MRI scanner (Siemens Medical Systems, Erlangen, Germany) using the standard head coil.

For functional imaging of the visual paradigm, we used a gradient echo EPI sequence (1 volume = 16 axial slices parallel to the plane crossing the anterior and posterior commissure, repetition time/echo time [TR/TE] = 2000 ms/60 ms, flip angle [FA] = 90°, field of view [FoV] = 200 × 200 mm², voxel size = 3.13 × 3.13 × 5.0 mm³). Functional time series consisted of 240 volumes and lasted 480 s.

For functional imaging of the imagery paradigm, we used a gradient echo EPI sequence (1 volume = 10 axial slices parallel to the plane crossing the anterior and posterior commissure, repetition time/echo time [TR/TE] = 1300 ms/60 ms, flip angle [FA] = 90°, field of view [FoV] = 200 × 200 mm², voxel size = 3.13 × 3.13 × 5.0 mm³). Functional time series consisted of 400 volumes and lasted 520 s.

A 3D T1-weighted FLASH (Fast Low-Angle Shot) scan was recorded in the same session for each subject (voxel size = 1 × 1 × 1 mm³).

Subjects were asked to keep their eyes steady during scanning. Offline electrooculography recordings showed absence of differences in saccade rate between conditions.

Design

The two different conditions of the visual paradigm (visual angle and visual color discrimination) were tested in one session following the classical block design (four separate blocks in a pseudorandom order, each lasted 38 s and contained 18 stimuli, altogether eight blocks, interblock interval 10 scans (20 s)). Stimuli were delivered to a high luminance LCD projector (EIKI LC-6000). The images were back-projected onto a frosted screen positioned at the foot end of the scanner and viewed by the subjects through a mirror placed on the head coil.

The imagery condition of the mental clock task was presented in one session during an fMRI run of 520 s (400 scans) on the basis of an event-related design. The session consisted of 23 tasks with a resting period between the tasks of 16 scans (20.8 s). Stimuli were digitized and presented in pseudorandom order using a custom-made MR-compatible auditory stimulation device.

Prior to the fMRI scanning sessions, vitamin E capsules were used to mark the positions of the international 10–20 EEG system on the scalp of each subject as a reference for the TMS coil positioning in the second part of the study.

Statistical Analyses

fMRI data analysis and visualization were performed using the Brain-Voyager 4.4 software package. Spatial and temporal smoothing, removal of linear trends, 3D motion correction, Talairach transformation of 3D anatomical data sets, and generation of 3D functional data sets (volume time courses) followed procedures published elsewhere (Goebel et al., 1998; Linden et al., 1999).

The statistical analysis of the variance of the BOLD signal was based on the application of multiple regression analysis to time

series of task-related functional activation (Friston et al., 1995). The general linear model (GLM) of the experiment was computed from the six (one for each subject) z-normalized volume time courses. Z normalization of the BOLD signal was performed subject by subject for each voxel time course.

For the visual paradigm, the signal values during the angle and color discrimination task were considered the effects of interest. The corresponding predictors, obtained by convolution of an ideal box-car response (assuming the value 1 for the time points of task presentation and the value 0 for the remaining time points) with a linear model of the hemodynamic response (Boynton et al., 1996), were used to build the design matrix of the visual paradigm.

During the mental paradigm, the mental processes following the acoustic presentation of the clock times were the effects of interest. Based on the individual response time of each subject, an appropriate set of predictors were created starting with stimulus onset as predictor 1, followed by a separate predictor for every following scanning volume (every 1.3 s), ending with the volume/predictor corresponding to the time point of the subject's button press (see Formisano et al., 2002). The design matrix of the mental paradigm was based on a convolution of the ideal box-car response function of these predictors with a linear model of the hemodynamic response (Boynton et al., 1996). The global level of the signal time courses in each session was considered to be a confounding effect.

To analyze the effects of each separate condition, 3D group statistical maps were generated by associating each voxel with the *F* value corresponding to the specified set of predictors and calculated on the basis of the least mean squares solution of the GLM. The obtained *p* values were corrected for multiple comparisons using a cortex-based Bonferroni adjustment. This adjustment represents a very conservative correction for multiple comparisons because it discounts spatial correlations amongst the error terms. The statistical group maps are based on a fixed effects analysis and thus pertain only to the subjects investigated in this study.

For significantly activated voxels, the relative contribution *RC* of the two visual paradigm conditions in explaining the variance of a voxel time course were computed as $RC = R_{extra}^{(2)} - R_{extra}^{(1)} / R_{extra}^{(2)} + R_{extra}^{(1)}$, where $R_{extra}^{(2)}$ is the contribution of the angle discrimination task predictor to the model and $R_{extra}^{(1)}$ is the contribution of the color discrimination predictor. The contribution of a (set of) predictor(s) to a model is computed as an incremental multiple correlation coefficient, R_{extra} , according to the "extra sum of squares principle" (Draper and Smith, 1998). The formula ensures that the parameter *RC* lies in the interval [-1,1]. An *RC* value of 1 (color coded red) indicates that a voxel time course is solely explained with predictor 1 (angle discrimination) whereas an *RC* value of -1 (color coded blue) indicates that a voxel time course is explained solely with predictor 2 (color discrimination). In the contrast maps of the visual paradigm, only *RC* values greater than 0.7 were visualized.

In the mental imagery paradigm, a relative latency map was generated in order to obtain a color-coded visualization of the onset latency of activated brain areas during the mental clock task (see Formisano et al., 2002).

Statistical results were then visualized through projecting 3D statistical maps on an axial cut of the anatomical data set that show the position of the vitamin E capsules indicating P3 and P4.

rTMS Experiment

Subjects

Sixty subjects volunteered to participate (mean age: 28.4 years, SD = 7.3; 23 males, 37 females). The subjects were randomly assigned to one of three groups (see Design). Twenty subjects were assigned to stimulation group "stim P4" (mean age: 28.3 years, SD = 8.3; 6 males, 14 females), twenty to stimulation group "stim P3" (mean age: 27.7 years, SD = 5.7; 12 males, 8 females), and twenty to the control group "sham" (mean age: 29.2 years, SD = 8; 5 males, 15 females).

Apparatus and Procedure

A custom TMS stimulator (MagPro, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) was used to generate repetitive biphasic magnetic pulses. Magnetic pulses were delivered with a figure-eight-coil (Magnetic Coil Transducer MC-B70, Medtronic) with an outer radius of 50 mm. Individual motor thresholds were

identified by stimulating the motor cortex with single TMS pulses until a movement of the contralateral thumb was detected in relaxed muscle state. For real rTMS, the center of the coil was held tangentially to the skull over P3 or P4, respectively (corresponding to left and right superior IPS, as revealed by the MR measurements). For sham rTMS, the coil was moved downwards from Pz by 3 cm and rotated so that the edge of the two wings of the coil rested at 90° on the scalp. In this sham rTMS condition, the induced magnetic field did not enter the brain, although the touch on the scalp and the sound of the coil being activated are comparable to those in the real rTMS condition (Kosslyn et al., 1999).

During the experiment, the coil was fixed in position and subjects were asked to keep their eyes steady throughout the experiment. Repetitive TMS was delivered at 110% of the subject's motor threshold, a field intensity sufficient to influence cortical activity (Ziemann et al., 1996), at 1 Hz stimulation frequency, in a single train of 12 min duration, in accordance with international safety standards of rTMS experimentation (Wassermann, 1998). Overall, each subject received 720 stimuli. These stimulation parameters produce effects that last beyond the stimulation period (Hallett, 2000; Kosslyn et al., 1999).

Design

Each of the two conditions in the visual paradigm (angle and color discrimination) consisted of five blocks, each containing 21 stimuli (210 stimuli) with eight of the presented clocks being target stimuli (38%).

The mental clock condition also consisted of five blocks, each containing a series of eight tasks (acoustical time pairs); in half of the tasks, the hands of the first imagined clock formed the greater angle and in the other half, the hands of the second imagined clock formed the greater angle (40 stimuli in total). Therefore, the whole sequence consisted of 250 stimuli. Before every block, the target-defining cue was presented. The trial sequence of the blocks as well as the sequence within each block were randomized.

Subjects were randomly assigned to one of three groups. One group was stimulated with real rTMS over P3 (stim P3), one was stimulated over P4 (stim P4), and one group received sham rTMS stimulation (sham).

We repeatedly measured the subject's performance in the three different tasks (visual angle discrimination, visual color discrimination, mental clock task) at four different times of measurement: as a pretest, during TMS (stimulation), immediately after TMS (posttest 1), and 12 min after TMS (posttest 2). In order to control for possible effects of rTMS on motor response, we included a finger tapping task for both hands at all four times of measurement in all groups.

Statistical Analyses

Mean reaction times for correctly detected target stimuli and mean error rates for undetected targets as well as falsely detected nontargets were computed by group and time of measurement separately for every task. A one-way ANOVA was computed to test for a significant difference between the groups at any of the four different times of measurement in the tasks, including a Scheffé procedure to test for significant single contrasts within the group factor. Additionally a two-way ANOVA for repeated measurements was computed in which the time of measurement was included as a separate factor in order to test for significant interactions between the group factor and the time of measurement. In further analyses, the gender as well as the handedness of the subjects were separately included as independent factors within a three-way ANOVA in order to test for possible interactions of second order (e.g., gender × group × time of measurement).

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