Hemispheric differences in the voluntary control of spatial attention: direct evidence for a right-hemispheric dominance within frontal cortex

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Hemispheric Differences in the Voluntary Control of Spatial Attention: Direct Evidence for a Right-Hemispheric Dominance within Frontal Cortex

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Abstract

■ Lesion studies in neglect patients have inspired two competing models of spatial attention control, namely, Heilman's "hemispatial" theory and Kinsbourne's "opponent processor" model. Both assume a functional asymmetry between the two hemispheres but propose very different mechanisms. Neuroimaging studies have identified a bilateral dorsal frontoparietal network underlying voluntary shifts of spatial attention. However, lateralization of attentional processes within this network has not been consistently reported. In the current study, we aimed to provide direct evidence concerning the functional asymmetry of the right and left FEF during voluntary shifts of spatial attention. To this end, we applied fMRI-guided neuro- navigation to disrupt individual FEF activation foci with a longer-lasting inhibitory patterned TMS protocol followed by a spatial cueing task. Our results indicate that right FEF stimulation impaired the ability of shifting spatial attention toward both hemifields, whereas the effects of left FEF stimulation were limited to the contralateral hemifield. These results provide strong direct evidence for right-hemispheric dominance in spatial attention within frontal cortex supporting Heilman's "hemispatial" theory. This complements previous TMS studies that generally conform to Kinsbourne's "opponent processor" model after disruption of parietal cortex, and we therefore propose that both theories are not mutually exclusive. ■

INTRODUCTION

Voluntary control of spatial attention is an important mechanism that allows prioritizing one location of the visual field to focus on relevant incoming sensory information. In healthy human volunteers, brain imaging techniques such as PET and fMRI have identified activity in frontal, parietal, and subcortical brain regions during tasks requiring shifts of spatial attention (Corbetta & Shulman, 2002). After stroke or brain injury, damage to those regions frequently causes spatial neglect, a neurological syndrome characterized by the failure to attend, explore, and act upon the contralesional side of space (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). Spatial neglect is more common and severe after damage to the right hemisphere, suggesting a hemispheric asymmetry of the mechanisms underlying spatial attention (Mesulam, 1981). On the basis of lesion findings, two models of spatial attention have emerged over the years, both accounting for this asymmetry but proposing very different mechanisms. According to Heilman's "hemispatial" theory, the right hemisphere is dominant in spatial attention, mediating attention shifts to both hemifields, whereas the left hemisphere exclusively mediates attention shifts to the contralateral hemifield (Heilman & Van Den Abell, 1980). In contrast, Kinsbourne's "opponent processor" model suggests that each hemisphere biases attention to the contralateral hemifield, with the rightward bias of the left hemisphere being stronger, and that both hemispheres are kept in balance because of interhemispheric competition (Kinsbourne, 1977).

Despite the fact that both theories propose very different mechanisms of spatial attention control, neuroimaging studies thus far have failed to provide consistent evidence in favor of either view (Corbetta & Shulman, 2011). Mostly, bilateral activation is reported in the dorsal fronto-parietal network including the FEF and the intraparietal sulcus (IPS), neither supporting the notion of a contralateral bias nor of right-hemispheric dominance (Shulman et al., 2010; Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005; Hopfinger, Buonocore, & Mangun, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). However, a contralateral bias is sometimes observed (Szczepanski, Konen, & Kastner, 2010), and topographic representations of the contralateral hemifield within the dorsal network (Silver & Kastner, 2009) lend some support to the "opponent processor" model. Conversely, evidence in favor of the "hemispatial" theory has also been reported recently (Sheremata, Bettencourt, & Somers, 2010). Beyond these inconsistencies, neuroimaging studies have been criticized on general grounds when assessing functional asymmetries (e.g., Macaluso &

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Patria, 2007), and caution is required when inferring the functional role of brain areas based on task-correlated activation alone.

In recent years, TMS has proven to be a valuable complementary method for the noninvasive study of structure–function relationships (Sack, 2006). Several studies have already successfully used TMS over parietal and frontal cortex to disrupt attentional processes (for a review, see Chambers & Mattingley, 2005). Neglect-like symptoms are frequently observed after parietal cortex stimulation, and the evidence so far is in favor of Kinsbourne's "opponent processor" model (Silvanto, Muggleton, Lavie, & Walsh, 2009; Dambeck et al., 2006; Hilgetag, Theoret, & Pascual-Leone, 2001; Seyal, Ro, & Rafal, 1995). For example, Hilgetag et al. (2001) found contralateral impairments and ipsilateral enhancements of target detection after 1-Hz rTMS over left and right IPS, conforming to Kinsbourne's notion of a contralateral bias and interhemispheric competition. In accordance with this interpretation, Dambeck et al. (2006) revealed that target detection is unaffected when TMS is applied simultaneously over left and right parietal cortex, whereas unilateral TMS impairs detection of contralateral stimuli. Frontal brain areas, on the other hand, have received far less attention, but TMS studies generally support an involvement of FEF in tasks with attentional components. TMS over FEF has been shown to affect reorienting of attention (Smith, Jackson, & Rorden, 2005), inhibition of return (Ro, Farnè, & Chang, 2003), and visual search (Muggleton, Juan, Cowey, & Walsh, 2003). However, the functional asymmetry between hemispheres has rarely been addressed, and those studies that directly compared the functional role of right and left FEF were unable to dissociate attentional from perceptual effects (Silvanto, Lavie, & Walsh, 2006; Grosbras & Paus, 2002, 2003). With this limitation in mind, TMS over frontal areas has produced results that are in favor of Heilman's "hemispatial" theory, contrasting the findings in parietal cortex discussed above. For example, it has been shown that right FEF stimulation increases perceptual sensitivity in both hemifields, whereas left FEF stimulation effects are limited to the contralateral hemifield (Grosbras & Paus, 2003). The same pattern of results has been observed in terms of changed phosphene thresholds when assessing the top–down influence of FEF on cortical excitability in extrastriate cortex (Silvanto et al., 2006).

In the current study, we aimed to provide direct evidence concerning the functional role of and hemispheric asymmetry between left and right FEF during voluntary spatial attention shifts that may differentiate between competing models of spatial attention control. To this end, we used fMRI to first identify right and left FEF in each of 20 healthy participants and then applied fMRI-guided neuronavigation to disrupt individual FEF activation foci with a longer-lasting inhibitory patterned TMS protocol. Following these experimentally induced "virtual lesions," participants were required to perform a spatial cueing task specifically designed to trigger covert spatial attention shifts and to separate orienting from reorienting of attention.

METHODS

Participants

Twenty participants (14 women, 6 men; aged 19–28 years) were recruited from the Maastricht University community. All were right-handed, had normal or corrected-to-normal vision, and had no history of neurological or psychiatric illness. Written informed consent was obtained before participation, and the study was approved by the local medical–ethical committee. Additionally, each participant was screened for fMRI and TMS experimentation safety by an independent medical supervisor.

Stimuli and Task

Participants performed a detection task with central symbolic cues (Figure 1) prompting covert shifts of attention to the expected target location (Posner, 1980). A fixation cross was continuously presented at the center of the screen. Cues consisted of two arrowheads flanking the fixation cross and pointed either to the left ($<+<$), to the right ($>+>$), or in opposite directions ($<+>$). Gabor patches (spatial frequency = 1.5 cycles per degree, envelope standard deviation = 0.75°, Michelson contrast = 60%; random orientations) were used as target stimuli and presented either left or right of the fixation cross at 7° eccentricity. Participants were instructed to press the space bar on a standard keyboard with the right index finger as fast as possible whenever a target was detected irrespective of target location and orientation. Catch trials without a target stimulus were included to prevent anticipatory responses. Stimuli were presented on a gamma-corrected 17-in. TFT screen (Samsung
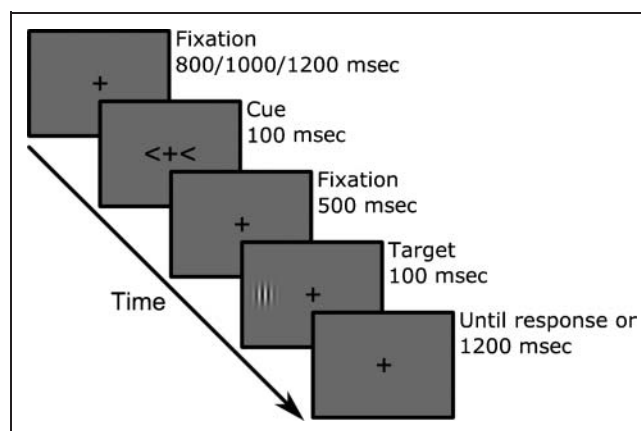
Figure 1. The sequence and timing of events for one possible trial is shown. In this case, the cue points to the left, prompting the participant to covertly shift attention to the left hemifield, and the target appears at the cued location (valid trial). A description of the other cue/target combinations is given in the main text.

SyncMaster 931 DF) at 57-cm viewing distance. The video mode was 1280 × 1024 at 60 Hz, and background luminance was 25 cd/m². The Presentation software package (NeuroBehavioral Systems, Albany, CA) was used to control stimulus presentation and recording of behavioral responses.

The task consisted of nine conditions that resulted from the combination of three cues (left, right, neutral) and three target locations (left, right, none/catch). Trials in which the cue provided valid information about the target location were more frequent than invalid trials (80% predictive validity) so that utilization of the cue was behaviorally beneficial. In neutral trials, the cue provided no information about the target location. Conceptually, neutral trials serve as a baseline condition that matches valid and invalid trials in terms of perceptual processing, target detection, and the behavioral response but lacks attentional components based on spatial expectancies. Trials with directional cues, however, allow covert shifts of spatial attention to the expected target location. In case of valid trials, RTs are typically faster compared with neutral trials (attentional benefits) indicating more efficient processing because of successful voluntary attention shifts. In case of invalid trials, RTs are typically slower compared with neutral trials (attentional costs) indicating that incorrect information about the target location requires reorienting of attention to the unexpected target location after target appearance. Taken together, this task isolates different attentional processes in a well-controlled way and allows measuring these processes in terms of RT differences between neutral and valid/invalid trials.

Each trial started with a cue presented for 100 msec indicating where the target stimulus was most likely to appear. At 600 msec after cue onset, the target stimulus was presented for 100 msec followed by a 1200-msec response window. The trial was terminated immediately after a button press, and there was an intertrial interval of either 800, 1000, or 1200 msec. Participants received corrective feedback (an error message on the screen) in case of false alarms, misses, anticipatory responses (RT below 100 msec or button press within the cue-target interval), or very slow responses (RT above 800 msec).

fMRI

Anatomical and functional data were acquired for each participant to allow precise localization of individual stimulation sites. The FEF localizer consisted of a simple block design with alternating blocks of central fixation and saccadic eye movements. During saccadic eye movement blocks, every 500 msec, a circle appeared at one of eight predefined locations along the horizontal or vertical meridian, and participants were instructed to track these circles with the eyes. In total, participants completed 21 blocks, each lasting 16 sec. Although this study focused on the role of the FEF in spatial attention, we have chosen for localization based on eye movements. Concep-

tually, this is closer to the original definition of the FEF (for a historical overview, see Amiez & Petrides, 2009). Moreover, eye movement-related BOLD signal changes in FEF are more robust compared with attention-related activation changes allowing easier and more time-efficient localization (De Haan, Morgan, & Rorden, 2008). Several studies have confirmed the involvement of the FEF in both spatial attention and eye movements, and neuroimaging studies generally report overlapping clusters of activation (De Haan et al., 2008; Corbetta et al., 1998).

Imaging was performed with a Siemens Allegra 3.0-T scanner equipped with a standard head coil (Siemens Medical Systems, Erlangen, Germany). High-resolution anatomical images covering the whole head were collected with a T1-weighted 3-D ADNI MPRAGE sequence (192 sagittal slices, matrix = 256 × 256, field of view = 256 × 256 mm, slice thickness = 1 mm, no gap, in-plane voxel size = 1 × 1 mm, flip angle = 9°, repetition time = 2250 msec, echo time = 2.6 msec). Functional images were obtained using a T2*-weighted single shot EPI sequence (32 oblique slices with full-brain coverage, matrix = 64 × 64, field of view = 192 × 192 mm, slice thickness = 3 mm, no gap, in-plane voxel size = 3 × 3 mm, flip angle = 90°, repetition time = 2000 msec, echo time = 30 msec). Visual stimuli were back-projected on a screen at the rear end of the scanner bore and could be seen by the participants via a mirror system attached to the head coil.

Data were preprocessed and analyzed using the Brain-Voyager QX 2.3 software package with default settings (Brain Innovation, Maastricht, The Netherlands). Anatomical data were corrected for intensity inhomogeneities and transformed to Talairach space (Talairach & Tournoux, 1988). Then, a reconstruction of the cortical surface was created for both hemispheres to support TMS coil positioning by improving the visualization of the anatomical gyrification. The first two volumes of the functional data were discarded because of T1 saturation effects. Preprocessing steps included slice scan time correction, 3-D motion correction, and high-pass filtering (two cycles). Then, functional data were coregistered with the anatomical data. Finally, the general linear model was used for statistical analysis, and the FEF was identified as the most significant cluster around the precentral sulcus and superior frontal sulcus in each hemisphere (see Figure 2A–D for an example). No further group analysis was performed because the localizer was used to identify activation foci for each participant to guide TMS coil positioning on an individual basis (Figure 2E).

TMS

TMS was applied using a Medtronic MagPro X100 stimulator (Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) and a figure-of-eight TMS coil (MC-B70; inner radius = 10 mm, outer radius = 50 mm). During each TMS session, continuous theta burst stimulation was applied for 40 sec (600 pulses, 50-Hz triplets in a 5-Hz

Figure 2. A, B, and C show the activation cluster of the right FEF for one representative participant in a sagittal, coronal, and transverse section of the brain, respectively. D shows the same cluster projected on a reconstruction of the cortical surface with the central sulcus on the left and the FEF at the junction of the precentral sulcus and superior frontal sulcus. E shows a snapshot of the neuronavigation system used to guide TMS coil positioning in real time with the red beam indicating where the magnetic field is strongest.
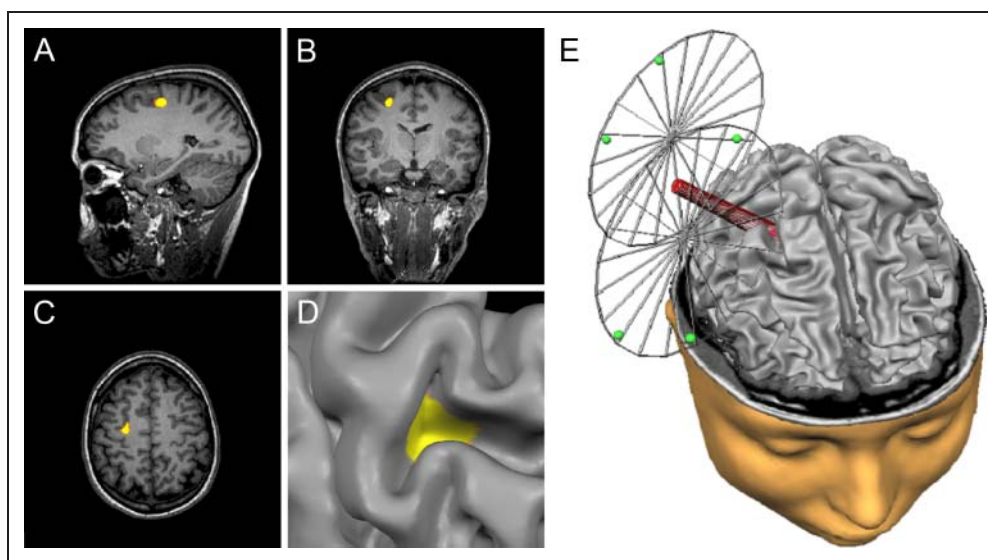
rhythm) over one of the three stimulation sites. This protocol has previously been shown to decrease cortical excitability and is commonly thought to have long-lasting effects of up to 1 hr (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Stimulation intensity was set at 80% of the individual resting motor threshold (mean: 26.4% of maximum stimulator output, range = 19%–37%). The motor threshold was determined using single pulse TMS over the right motor cortex. It was defined as the smallest intensity that elicited a visible muscle twitch in the contralateral index finger in three of six trials. None of the participants reported any adverse side effects of the stimulation.

The BrainVoyager TMS Neuronavigator system (Brain-Innovation, Maastricht, The Netherlands) was used to ensure precise coil positioning (Figure 2E). This frameless stereotactic system allows real-time visualization of the TMS coil relative to individual brain anatomy and functionally defined target points based on fMRI data. We used this system to navigate the TMS coil to the optimal position for targeting individual activation foci in each participant. The TMS coil was manually held perpendicular to the skull, and the distance between the center of the coil and target point was kept as small as possible. For the left and right FEF, the coil was oriented parallel to the precentral sulcus with the coil handle pointing lateral. In case of vertex stimulation, the coil was oriented in line with the longitudinal fissure and the coil handle pointed posterior.

Procedure and Design

Before the main experiment, all participants completed a pilot session that was identical to subsequent sessions with the exception that no TMS was applied. The purpose of this session was to assess whether participants made use of the information provided by the cues. Participants were only invited for the remaining experiment in case of statistically significant cueing effects. More specifi-

cally, we checked for the presence of attentional benefits and costs indicating shifts of spatial attention after the cue and reorienting of spatial attention after target appearance at an unexpected location, respectively. The task was performed as expected by 20 participants, and only one participant was excluded because cues were ineffective in modulating behavior.

We used a full within-subject design so that all participants received TMS to the right FEF, left FEF, and vertex. Vertex stimulation was considered a control condition where no effects on task performance were expected. All TMS sessions were identical except for the stimulation site, and the order of sessions was counterbalanced across participants. To prevent carry-over effects, TMS sessions were separated by at least 1 day without TMS. During TMS sessions, participants were comfortably seated in a chair with the head supported by a chin rest. TMS was applied after completion of 72 practice trials, immediately followed by the spatial attention task. In total, participants completed 10 blocks, each consisting of 72 trials presented in randomized order. Including short breaks between blocks, the overall duration of the behavioral task never exceeded 35 min. The proportion of valid, invalid, neutral, and catch trials in each experimental block was 8:2:5:3, resulting in 320 valid trials, 80 invalid trials, 200 neutral trials, and 120 catch trials per TMS session. At the beginning of a block, four additional practice trials were included that were not considered in the analysis. Between blocks, participants received feedback about their average performance to ensure that they were motivated throughout the session.

Eye Movement Control

EOG was used during task execution to allow off-line control of fixation performance. Data were recorded bipolarly from two pairs of Ag–AgCl electrodes with a

BrainAmp ExG system (BrainProducts GmbH, Munich, Germany). Eye movements and eye blinks were monitored with electrodes positioned at the outer canthus of each eye (horizontal EOG) and above and below the right eye (vertical EOG). Additionally, a reference electrode was placed on the mastoid behind the right ear. The impedance of all electrodes was kept below 5 kΩ. The EOG signal was digitized at 1000 Hz, high-pass filtered at 0.1 Hz, and stored on disk using BrainVision Recorder (BrainProducts GmbH, Munich, Germany). Offline data analysis was performed with BrainVision Analyzer (BrainProducts GmbH, Munich, Germany). Single trial data were visually inspected, and all trials contaminated by eye movements or eye blinks between cue appearance and button press were excluded from further analysis. This was necessary because eye movements indicate that participants potentially failed to covertly shift their attention to the cued location and eye blinks can interfere with the perception of the cue and target.

Statistical Analysis

Two participants were excluded from the analysis because of excessive eye movements (more than 20% of all trials). For the remaining 18 participants, all trials contaminated by eye movements or eye blinks were discarded. Additionally, trials were regarded as incorrect and removed in case of false alarms, misses, anticipatory responses, or very slow responses. Because participants received corrective feedback after incorrect responses, subsequent trials were excluded as well to allow reconcentration on the task. Trials following invalid trials were removed to counteract sequence effects. Benefits and costs have been shown to be reduced after invalid trials because of strategic changes in the utilization of the cue (Jongen & Smulders, 2007). Outliers were excluded according to the 1.5 × Interquartile range criterion. After application of these exclusion criteria, 78% of all trials

remained and were used to compute individual median RTs. Across all conditions, the proportion of excluded trials never dropped below 75%, and there were no systematic differences between conditions. On the individual level, median RTs were always based on at least 20 trials per condition. Individual median RTs were submitted to a three-way repeated-measures ANOVA with Stimulation Site (right FEF, left FEF, vertex), Cue Validity (valid, neutral, invalid), and Hemifield (left, right) as within-subject factors. Post hoc pairwise comparisons were corrected for multiple comparisons by Fisher's least significant difference procedure.

RESULTS

fMRI-based Localization of TMS Target Points

All participants completed a functional localizer during an fMRI session to precisely identify the right and left FEF on an individual basis. This approach accounts for interindividual differences in FEF localization and allows optimal TMS coil positioning even when functional regions do not correspond to the macro-anatomical organization of the brain. Data for the right FEF of one representative participant are shown in Figure 2, together with an illustration of the neuronavigation system used to monitor the exact coil position in real time.

To allow comparisons with other studies, we transformed individual target points to Talairach space (Figure 3B) and calculated the average coordinates of the right FEF (28, −8, 48) and left FEF (−25, −8, 50). These were very similar to FEF coordinates reported in previous neuroimaging studies (Shulman et al., 2009; Kincade et al., 2005). Moreover, the variability of target points across participants was assessed in terms of their Euclidian distance from the average target point (Figure 3A and C). The average displacement across all participants was 7 mm for the right FEF and 8 mm for the left FEF with deviations ranging from 2 to 15 mm for both stimulation sites. Taken together,

Figure 3. B depicts TMS target points projected on a mesh of a reconstructed head in Talairach space. For the right and left FEF, individual target points are shown in red and green, respectively. For the vertex condition, only the average target point is shown in blue. A and C illustrate deviations from the average target point across participants for the right and left FEF, respectively. In both 3-D plots, data are centered around its mean (yellow), and individual target points are plotted according to their displacement in the x, y, and z direction in Talairach space on a millimeter scale.
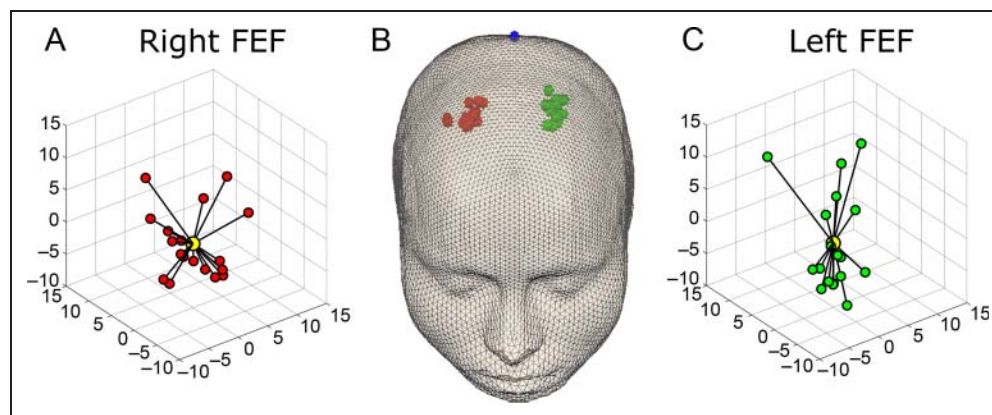
Table 1. RTs (in Milliseconds) and Standard Error of Mean (in Parentheses) for Each Experimental Condition

TMS	Left Hemifield			Right Hemifield		
	Right FEF	*Left FEF*	*Vertex*	*Right FEF*	*Left FEF*	*Vertex*
Valid	267 (7.3)	260 (5.7)	261 (9.1)	264 (7.0)	259 (6.9)	256 (8.9)
Neutral	283 (7.2)	280 (7.1)	282 (9.5)	275 (7.6)	268 (6.4)	271 (9.6)
Invalid	315 (8.4)	312 (9.7)	305 (11.2)	305 (7.3)	300 (9.2)	304 (10.9)
Benefits	15.4 (3.0)	20.4 (4.0)	20.9 (3.2)	11.2 (2.2)	9.1 (2.4)	15.1 (2.5)
Costs	32.4 (4.9)	31.2 (5.1)	22.3 (4.2)	29.7 (4.8)	32.7 (6.1)	32.5 (5.7)

this indicates that, although individual target points were closely clustered, interindividual differences in FEF localization were notable and likely of practical relevance when it comes to precise application of TMS (Sack et al., 2009).

Errors and Eye Movements

Participants were able to perform the task at high levels of accuracy during all sessions. The mean accuracy was 98.0%, 97.8%, and 98.1% after stimulation of the right FEF, left FEF, and vertex, respectively. A repeated-measures ANOVA confirmed that Accuracy did not differ significantly between sessions ($F(2, 34) = 0.249, p > .70$). Similarly, the occurrence of eye movements and eye blinks was unaffected by TMS ($F(2, 34) = 2.102, p = .138$). Only 5.5% of all trials were discarded because of these breaks of central fixation with mean values of 6.2%, 5.5%, and 4.9% for the right FEF, left FEF, and vertex stimulation, respectively. Most importantly, this indicates that our results are not confounded by effects of FEF stimulation on eye movement control.

Effect of TMS on RTs

A repeated-measures ANOVA on median RTs (see Table 1) with Stimulation Site (right FEF, left FEF, vertex), Cue (valid, neutral, invalid), and Hemifield (left, right) as within-subject factors revealed significant main effects of Cue ($F(2, 34) = 55.390, p < .0001$) and Hemifield ($F(1, 17) = 10.119, p < .01$). The main effect of Cue resulted from the typical orienting effects observed in spatial cueing tasks. To obtain an unbiased estimate of task performance under baseline conditions, we then statistically tested the effect of cue in the vertex condition, undistorted by potential effects of FEF stimulation (Figure 4). Compared with neutral trials, faster RTs were observed on valid trials (benefits, $t(17) = 7.450, p < .0001$), and slower RTs were observed on invalid trials (costs, $t(17) = 5.961, p < .0001$). This strongly indicates that participants made correct use of the cues by performing covert voluntary shifts of spatial attention toward the cued location. Moreover, the presence of both benefits and costs allows segregating dif-

ferent subprocesses of attentional control and is therefore a prerequisite for investigating differential effects of TMS on attentional orienting and reorienting, respectively. The main effect of Hemifield resulted from generally faster RTs for stimuli in the right hemifield. Given that participants always had to respond with their right hand, this most likely is an instance of the Simon effect (Simon & Rudell, 1967). Most importantly, we also found a significant three-way interaction between Stimulation Site, Cue, and Hemifield ($F(4, 68) = 2.748, p < .05$), which was then further explored in terms of benefits (difference in RT between neutral and valid trials) and costs (difference in RT between neutral and invalid trials) within each hemifield for all stimulation sites. The main effect of Stimulation Site and the two-way interactions were not significant because of this higher-order interaction.

Effect of TMS on Benefits

We first examined the effects of right and left FEF stimulation on attentional benefits (see Table 1) compared with vertex stimulation with paired *t* tests. After right FEF stimulation (Figure 5A), we found a significant reduction of benefits in the left hemifield ($t(17) = 2.585, p < .05$) as well as in the right hemifield ($t(17) = 2.257, p < .05$). After left FEF stimulation (Figure 5B), however, we only found a significant reduction of benefits in the right
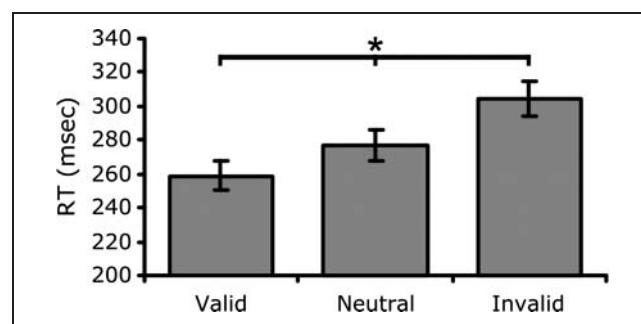
Figure 4. RT data for the vertex condition showed the expected effect of cue validity with robust attentional benefits and costs. All pairwise comparisons are statistically significant at an alpha level of .0001, and error bars depict standard errors.
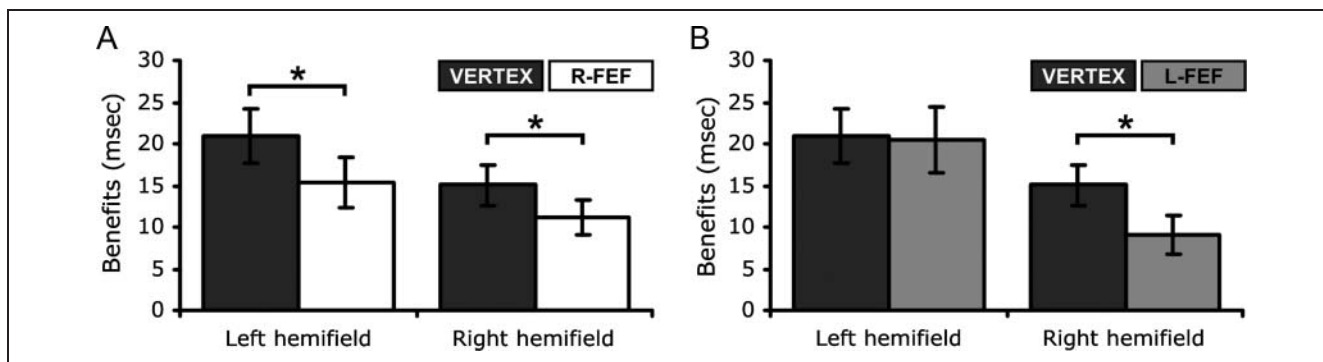
Figure 5. Attentional benefits for each hemifield after TMS over the right FEF (A) and the left FEF (B) compared with vertex stimulation. Attentional benefits are defined as the difference in RT between neutral and valid trials. Reduced benefits indicate impaired shifts of spatial attention. Differences marked with an asterisk are statistically significant at an alpha level of .05, and error bars depict standard errors.

hemifield ($t(17) = 2.304$, $p < .05$). Benefits in the left hemifield were unaffected by TMS over the left FEF ($t(17) = 0.140$, $p > .80$). In summary, both right and left FEF stimulation impaired the ability of shifting spatial attention toward the respective contralateral hemifield, as measured by significantly reduced attentional benefits. However, only TMS over the right FEF also significantly impaired spatial attention shifts toward the ipsilateral right hemifield, and thus resulted in bilateral spatial deficits, whereas the effects of left FEF stimulation were limited to the contralateral hemifield.

Effect of TMS on Costs

We then examined the effects of left and right FEF stimulation on attentional costs (see Table 1) compared with vertex stimulation. After right FEF stimulation (Figure 6A), we found a significant increase of costs in the left hemifield ($t(17) = 2.175$, $p < .05$) but not in the right hemifield ($t(17) = 0.520$, $p > .60$). After left FEF stimulation (Figure 6B), we found the same pattern of results with increased costs only in the left hemifield ($t(17) = 2.879$, $p < .05$) and no effect in the right hemifield ($t(17) = 0.044$, $p > .90$). In summary, both right and left FEF stimulation

impaired the ability of reorienting spatial attention to the unexpected target location, but the effects were limited to the left hemifield.

Effect of TMS on Neutral Trials

Finally, we examined the effects of left and right FEF stimulation on neutral trials compared with vertex stimulation. A repeated-measures ANOVA with Stimulation Site and Hemifield as within-subject factors revealed a significant main effect of Hemifield ($F(1, 17) = 15.134$, $p < .005$) resulting from generally faster RTs for stimuli in the right hemifield. However, there was no main effect of TMS ($F(2, 34) = 0.436$, $p > .60$) and no significant TMS × Hemifield interaction ($F(2, 34) = 1.335$, $p > .20$). This indicates that the effects of TMS on benefits and costs were contingent on spatial expectations based on directional cues and do not reflect a general impairment in target detection.

DISCUSSION

Voluntary spatial attention describes our ability to select one location of the visual field to enhance processing of
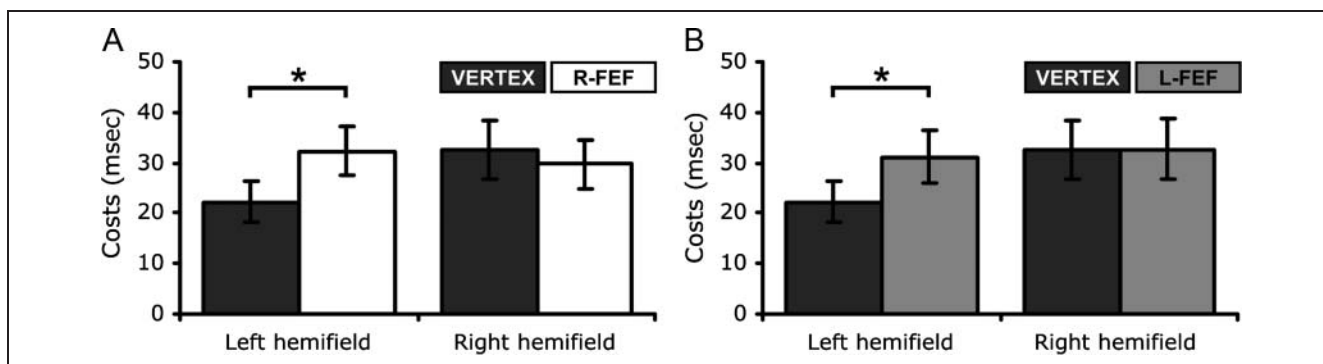
Figure 6. Attentional costs for each hemifield after TMS over the right FEF (A) and the left FEF (B) compared with vertex stimulation. Attentional costs are defined as the difference in RT between neutral and invalid trials. Increased costs indicate impaired reorienting of spatial attention. Differences marked with an asterisk are statistically significant at an alpha level of .05, and error bars depict standard errors.

relevant incoming sensory information. In healthy volunteers, neuroimaging studies have identified FEF and IPS as core nodes of a bilateral dorsal fronto-parietal network underlying spatial attention shifts. Accordingly, stroke and brain injuries within these regions are associated with spatial neglect, a neurological syndrome characterized by impaired attentional processes (Corbetta et al., 2005). Because spatial neglect is more common after damage to the right hemisphere, a functional asymmetry in the control of spatial attention between the two hemispheres is widely assumed, although the underlying mechanisms are still hotly debated (Szczepanski et al., 2010; Corbetta & Shulman, 2002). However, neuroimaging studies thus far have failed to consistently reveal lateralization of attentional processes within the dorsal fronto-parietal network (Corbetta & Shulman, 2011). In recent years, TMS has proven to be a valuable complementary method for the noninvasive study of structure–function relationships (Sack, 2006). Using a "virtual lesion" approach, the goal of this study was to investigate the role and functional asymmetry of the right and left FEF during voluntary shifts of spatial attention. We used a spatial cueing task specifically designed to trigger covert spatial attention shifts and assessed the behavioral consequences of right and left FEF disruption. A longer-lasting inhibitory patterned TMS protocol was applied to mimic a real lesion in healthy volunteers while benefiting from fMRI-guided neuronavigation allowing precise targeting of individual activation foci.

Using this approach of experimental perturbation, this study revealed that only disruption of the right FEF causes a reduction of attentional benefits in both hemifields, whereas disruption of the left FEF exclusively affects attentional benefits in the contralateral hemifield. This is, to the best of our knowledge, the first direct experimental evidence supporting the general notion of functional asymmetry between right and left frontal cortex in spatial attention as originally proposed by Mesulam (1981) and Heilman (1980). Furthermore, our findings bear direct implications for current functional–anatomical models of spatial attention, which have been discussed controversially in a recent review (Corbetta & Shulman, 2011). Although the involvement of FEF in voluntary control of spatial attention is undisputed (Corbetta & Shulman, 2002), there is an ongoing debate between two competing theories of spatial attention control, namely Heilman's "hemispatial" theory (Heilman & Van Den Abell, 1980) and Kinsbourne's "opponent processor" model (Kinsbourne, 1977).

Our results provide strong direct evidence for right-hemispheric dominance in spatial attention supporting Heilman's "hemispatial" theory. According to this view, the right hemisphere mediates attention shifts to both hemifields, whereas the left hemisphere only mediates attention shifts to the contralateral right hemifield (Heilman & Van Den Abell, 1980). This functional asymmetry, as predicted by the model, completely matches the pattern of reduced attentional benefits reported here. In contrast, our results are at odds with Kinsbourne's "opponent

processor" model, which claims that each hemisphere biases attention to the contralateral hemifield (Kinsbourne, 1977). According to this view, a bilateral impairment, as observed after right FEF disruption, is unexpected and cannot be readily explained. At first glance, our results are therefore contrasting previous TMS findings that provided evidence in favor of Kinsbourne's model after disruption of parietal cortex (Silvanto et al., 2009; Dambeck et al., 2006; Hilgetag et al., 2001; Seyal et al., 1995). Although this might be perceived as inconsistent, the present findings rather indicate that parietal and frontal cortex have different functional properties. In this sense, Heilman's "hemispatial" theory and Kinsbourne's "opponent processor" model might not be mutually exclusive but rather apply to different nodes of the dorsal fronto-parietal network. The current findings, together with previous TMS studies, could lead the discussion for a combined model of spatial attention control that incorporates mechanisms of interhemispheric competition and right-hemispheric dominance.

It is noteworthy that the behavioral consequences of FEF stimulation reported here do not fully match the attentional deficits commonly observed in spatial neglect (Mesulam, 1981). More specifically, left hemisphere damage often leaves attentional processes largely intact presumably because the right hemisphere is still capable of shifting attention to both hemifields. Similarly, after right hemisphere damage, only attentional deficits are observed in the left hemifield presumably because the intact left hemisphere is still capable of shifting attention to the right hemifield. These compensatory abilities because of overlap in function were not observed with the "virtual lesion" approach used in this study. Although this mismatch might be perceived as an argument against the validity of the "virtual lesion" approach, it actually is a consequence of several advantages of the direct experimental disruption by TMS in healthy volunteers compared with lesion studies. First, behavioral deficits in neglect patients are normally assessed weeks after occurrence of the lesion (e.g., Corbetta et al., 2005) allowing for functional reorganization and compensatory processes, whereas TMS is applied immediately before task performance. Second, lesions are hardly ever restricted to one functional brain area and are subject to large interindividual variability (e.g., Mort et al., 2003). In contrast, TMS with fMRI-guided neuronavigation allows localization and targeting of individually defined functional brain areas (Sack et al., 2009). Third, TMS-induced disruption of normal brain functioning is limited in time so that full within-subject designs are possible where different "virtual lesions" can be studied in the same participants. Taken together, the "virtual lesion" approach overcomes several confounding factors inherent to lesion studies and can therefore be considered an elegant experimental approach to unmask the real functional role of brain areas in an undistorted way. Only under these conditions, it was possible to reveal the functional asymmetry between right and left FEF and to demonstrate right-hemispheric dominance in spatial attention.

It has to be emphasized that TMS specifically impaired attentional processes. RTs on neutral trials were unaffected by TMS, which rules out explanations in terms of general changes in target detection or perceptual effects because of modulations of visual cortex. This is in contrast with earlier studies that also investigated the behavioral consequences of FEF stimulation on spatial attention and target detection (Grosbras & Paus, 2002, 2003). Using a similar spatial cueing task with single pulse TMS before target appearance, bilateral effects after right FEF stimulation and contralateral effects after left FEF stimulation were reported, resembling the current findings (Grosbras & Paus, 2002). However, instead of disruption of attentional processes, a general facilitation across all cueing conditions was found, but attentional benefits were unaffected. Although this is an interesting finding in itself, such unspecific effects do not allow drawing conclusions about voluntary shifts of spatial attention, as they occur in a spatial cueing task, because attention shifts are generally operationalized in terms of attentional benefits, that is, the difference between valid and neutral trials. A follow-up study requiring detection of near-threshold visual stimuli indeed confirmed that FEF stimulation improves target detection per se when applied before target appearance (Grosbras & Paus, 2003). This is probably because of top–down modulations of visual cortex, as has been shown by the simultaneous combination of TMS and fMRI (Ruff et al., 2006). Consequently, studies investigating the role of FEF in spatial attention by means of "online" TMS, that is, applying TMS during task execution, struggle to dissociate attentional from perceptual effects. As demonstrated in the current study, the "virtual lesion" approach can have high functional specificity although it lacks the temporal specificity of online TMS. Nevertheless, a detailed exploration of FEF functioning over time covering the cueing phase and posttarget processing would be a welcome addition to the current findings and potentially reveal a level of detail that offline TMS cannot achieve.

We also observed increased attentional costs in the left hemifield after stimulation of the right and left FEF. This pattern of results differs from the effects of TMS on attentional benefits described above and, as such, certainly highlights the general involvement of FEF not only in voluntary shifts of spatial attention (attentional benefits) but also in reorienting of attention toward an unexpected target location (attentional costs). On first sight, this impairment in task performance might be counterintuitive because one could expect that the disruption of attentional benefits observed after FEF stimulation also leads to reduced attentional costs. With the initial allocation of attention toward the cued location being weaker, it seems plausible that the costs of reorienting decrease as well. However, such an effect could easily be overruled by a TMS-induced disruption of the reorienting process itself. In this sense, our results indicate that attentional costs are not simply the flip side of attentional benefits and that FEF stimulation differentially affects both processes. This

interpretation is supported by pharmacological studies showing a dissociation of attentional benefits and costs (Murphy & Klein, 1998; Witte, Davidson, & Marrocco, 1997; Clark, Geffen, & Geffen, 1989). This being said, we would like to remain rather conservative in drawing further conclusions regarding the specific functional asymmetry of FEF for the reorienting of spatial attention because of the following reason: Every invalid trial consists of an initial shift of attention to the cued location followed by reorienting of attention toward the unexpected target location. The effects of TMS on attentional benefits clearly demonstrate that the initial shift of attention is already impaired by TMS. Any effect of TMS on the reorienting process is therefore potentially confounded by this preceding disruption by TMS or, at least, cannot be dissociated from it based on RTs alone. Nevertheless, the effects of TMS on attentional benefits and costs do differ from each other, suggesting differential involvement of FEF in orienting and reorienting of spatial attention.

Regarding the interpretation of the present data, one important assumption is that the effects of TMS were confined to the stimulation site. In fact, many studies have established that TMS affects remote brain areas within the same functional network (Sack et al., 2007; Ruff et al., 2006; Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2005). In our case, stimulation of FEF might also disrupt other nodes of the dorsal and even ventral fronto-parietal network. However, it has to be emphasized that this possibility does not undermine our finding of functional asymmetry between the left and right hemisphere. Instead, this might only be problematic when it comes to attributing the effects to a particular brain region. Although we cannot exclude remote effects of TMS with certainty, it nevertheless seems likely that our behavioral effects are caused by direct FEF disruption. To begin with, in contrast to the effects of FEF disruption reported here, TMS over parietal cortex commonly produces effects that are more in line with Kinsbourne's "opponent processor" model (Silvanto et al., 2009; Dambeck et al., 2006; Hilgetag et al., 2001; Seyal et al., 1995). In our view, there are no fundamental differences between this study and previous work that can account for these diverging results except for the difference in stimulation sites. Consequently, it seems most plausible that the functional asymmetry revealed here is because of directly impaired FEF functioning. Furthermore, according to current functional–anatomical models of spatial attention, a spread of TMS effects to the ventral fronto-parietal network is not expected to have effects on voluntary shifts of spatial attention because this network is thought to mediate stimulus-driven attention (Corbetta & Shulman, 2002). This view is supported by a recent TMS study that reported intact voluntary shifts of spatial attention despite disruption of the right TPJ (Chica, Bartolomeo, & Valero-Cabré, 2011). Taken together, it seems unlikely that our findings are a result of TMS effects remote from the stimulation sites.

As already pointed out, neuroimaging studies have provided inconsistent results regarding the functional asymmetry of spatial attention within the dorsal fronto-parietal network. For that reason, a new framework has recently been put forward to explain the predominance of spatial neglect after right hemisphere damage (Corbetta & Shulman, 2011). In short, although the spatial deficits observed in neglect are closely related to the functional role of the dorsal network, damage outside this network seems to be their primary cause. The ventral fronto-parietal network is lateralized to the right hemisphere, and neglect is therefore considered to originate from there, but the dorsal network is affected as well (mainly in the right hemisphere) because of disrupted inter-actions between the two systems. The right hemisphere is no longer being argued to be dominant in spatial attention mainly because of the weak direct empirical evidence supporting this model in the past two decades. Our results illustrate the strength of noninvasive brain stimulation to reveal structure–function relationships where lesion studies and/or pure activation-based approaches might struggle. We show that it is premature to give up on the idea of right-hemispheric dominance in the dorsal network. Together with the strong empirical support for Kinsbourne's "opponent processor" model within parietal cortex, it seems most promising to combine both models and to further investigate functional differences within the dorsal fronto-parietal network.

Acknowledgments

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