Hemispheric Differences in Frontal and Parietal Influences on Human Occipital Cortex: Direct Confirmation with Concurrent TMS–fMRI

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Abstract

■ We used concurrent TMS–fMRI to test directly for hemispheric differences in causal influences of the right or left fronto-parietal cortex on activity (BOLD signal) in the human occipital cortex. Clinical data and some behavioral TMS studies have been taken to suggest right-hemisphere specialization for top–down modulation of vision in humans, based on deficits such as spatial neglect or extinction in lesioned patients, or findings that TMS to right (vs. left) fronto-parietal structures can elicit stronger effects on visual performance. But prior to the recent advent of concurrent TMS and neuroimaging, it was not possible to directly examine the causal impact of one (stimulated) brain region upon others in humans. Here we stimulated the frontal or intraparietal cortex in the left or right hemisphere with TMS, inside an MR scanner, while measuring with fMRI any resulting BOLD signal changes in visual areas V1–V4 and V5/MT+. For both frontal and parietal stimulation, we found clear differences between effects of right- versus left-hemisphere TMS on activity in the visual cortex, with all differences significant in direct statistical comparisons. Frontal TMS over either hemisphere elicited similar BOLD decreases for central visual field representations in V1–V4, but only right frontal TMS led to BOLD increases for peripheral field representations in these regions. Hemispheric differences for effects of parietal TMS were even more marked: Right parietal TMS led to strong BOLD changes in V1–V4 and V5/MT+, but left parietal TMS did not. These data directly confirm that the human frontal and parietal cortex show right-hemisphere specialization for causal influences on the visual cortex. ■

INTRODUCTION

It is increasingly recognized that visual processing within the occipital cortex may be influenced by areas outside the conventional visual system. For instance, it is often proposed that a putative fronto-parietal ''attention network'' may modulate visual processing via back-projection influences (Ruff & Driver, 2006; Serences & Yantis, 2006; Miller & D'Esposito, 2005; Driver, Eimer, Macaluso, & van Velzen, 2004; Driver, Vuilleumier, & Husain, 2004; Corbetta & Shulman, 2002; Frith, 2001; Hopfinger, Buonocore, & Mangun, 2000; Kastner & Ungerleider, 2000; Miller, 2000; Duncan, Humphreys, & Ward, 1997). This might potentially explain some clinical phenomena in humans, whereby lesions in frontal and/or parietal areas, well beyond the classical ''visual'' cortex, can lead to putatively attentional deficits that affect visual abilities, such as neglect or extinction (Milner & McIntosh, 2005; Mort et al., 2003; Karnath, Milner, & Vallar, 2002; Vuilleumier & Rafal, 2000; Mesulam, 1999; Driver & Mattingley, 1998). Such clinical phenomena are typically more common and pronounced after right- than left-hemisphere damage. This has been taken to suggest that the right frontal and parietal cortex might normally play special roles in influencing activity in the visual cortex for humans (e.g., see Deco & Zihl, 2004; Marzi, Girelli, Natale, & Miniussi, 2001; Marzi, Girelli, Miniussi, Smania, & Maravita, 2000; Mesulam, 1999, but see also Barceló, Suwazono, & Knight, 2000), that may differ from any influences from the left frontal or parietal cortex. Surprisingly, however, this has never been shown directly to date, due to a lack of methods for studying and comparing the causal impact of any particular brain area upon others in humans. Although extensive neuroimaging work on human visual attention has triggered considerable discussion about whether right-hemisphere frontal–parietal structures may be qualitatively or quantitatively special, when compared to left-hemisphere homologues in attention tasks (e.g., see Serences & Yantis, 2006; Driver, Eimer, et al., 2004; Driver, Vuilleumier, et al., 2004; Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000, for reviews), standard neuroimaging studies are not sufficient on their own to address hemispheric differences in truly causal impacts upon the visual cortex. Conversely, although stimulation methods such as transcranial magnetic stimulation (TMS; see below) are causal interventions, until recently, it has not been possible to combine such brain stimulation with

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neuroimaging in humans in order to study the impact of stimulating one area upon activity in others.

Recent advances in invasive animal work now allow for microstimulation (or other manipulations) of a targeted region to be combined with recordings from another interconnected area, as for example in the pioneering work of Armstrong and Moore (2007) and Moore and Armstrong (2003), who studied influences from the frontal eye field (FEF) upon monkey V4 (see also Winkowski & Knudsen, 2007, for a potentially related barn–owl study). But animals may not show the hemispheric asymmetries in function for the frontal and parietal cortex that have tentatively been attributed to humans based on clinical evidence (e.g., see Wardak, Ibos, Duhamel, & Olivier, 2006; Wardak, Olivier, & Duhamel, 2004). Moreover, to our knowledge, the monkey studies examining frontal influences on the visual cortex, to date, have typically assessed only the right hemisphere (Armstrong & Moore, 2007; Moore & Armstrong, 2003; Moore, personal communication).

Accordingly, here we capitalized on the recent development of concurrent TMS–fMRI in humans (e.g., Ruff et al., 2006; Baudewig et al., 2001; Bohning et al., 1999; Shastri, George, & Bohning, 1999), using this as a novel approach for probing directly whether the right versus left human frontal (or intraparietal) cortex can have qualitatively different causal influences on BOLD signal in the occipital visual cortex. Intriguingly, several purely behavioral TMS studies already suggest possible hemispheric differences in the impact of frontal or parietal TMS on visual processing, typically finding that right frontal or parietal TMS can have more marked influences on visual performance than TMS of corresponding left-hemisphere sites (e.g., Muggleton et al., 2006; Silvanto, Lavie, & Walsh, 2006; Chambers, Payne, Stokes, & Mattingley, 2004; O'Shea, Muggleton, Cowey, & Walsh, 2004; Grosbras & Paus, 2002, 2003; Muggleton, Juan, Cowey, & Walsh, 2003; Pourtois, Vandermeeren, Olivier, & de Gelder, 2001). However, such purely behavioral TMS effects leave it unclear whether the observed differences between left and right TMS reflect only local processing in the stimulated area, or rather the differential physiological impact of right versus left frontal or parietal regions in inducing causal changes in activity of remote visual cortex.

To address this, here we used TMS in combination with concurrent fMRI of retinotopic visual cortex, to characterize any physiological differences between the impact of right versus left frontal (or parietal) TMS upon BOLD activity in early visual cortex. We had recently introduced this combined TMS–fMRI approach, but had stimulated only right-hemisphere sites (Ruff et al., 2006, 2008; see also Taylor, Nobre, & Rushworth, 2007; Paus et al., 1997, for related uses of TMS in combination with other neuroimaging methods in humans). Here we ran two new experiments in which we applied the analogous stimulation protocol in the same participants, but now applying TMS to corresponding sites in the left hemisphere instead. This allowed us to directly compare, for the first time, the on-line causal effects of left- versus right-hemisphere frontal or parietal TMS upon BOLD activity in retinotopically mapped human occipital cortex. To anticipate the outcome, we observed profound differences in these influences, indicating specific neural mechanisms in right-hemisphere fronto-parietal areas for modulation of the visual cortex. We found that the impact of left frontal (or parietal) TMS upon BOLD signal in the visual cortex differed significantly from corresponding effects of right fronto-parietal TMS. Our data may thus offer a new type of explanation, in terms of remote physiological effects upon the visual cortex, for why TMS (or lesions) to the right-hemisphere frontoparietal cortex can often affect performance for visual tasks in a different (and typically more pronounced) fashion than corresponding left-hemisphere interventions.

METHODS

Experimental Rationale

In the two new experiments described here, we examined any influences of left frontal or left parietal TMS on activity in multiple striate and extrastriate visual areas of the human brain, as measured concurrently via the BOLD signal with fMRI. Crucially, these new data allowed direct, well-matched statistical comparisons to existing data on influences of TMS to corresponding frontal and parietal sites in the right cortical hemisphere (originally reported in Ruff et al., 2006, 2008; see below). This allowed us to compare the impact of left or right frontal/parietal TMS upon the human visual cortex for the first time. Inside an MR scanner, TMS was applied at four different intensities over either the left frontal cortex (at the putative location of the human FEF) or over the left parietal cortex (intraparietal sulcus, IPS). We concurrently measured with fMRI any BOLD changes in the occipital visual cortex that covaried with TMS intensity. Sensitivity for early visual regions (areas V1–V4 and V5/MT+) was maximized by using fMRI with an occipital surface coil, in combination with detailed retinotopic mapping of cortical visual areas for each individual participant. This allowed us to assess whether V1 and other retinotopic areas of the human visual cortex could be affected by TMS stimulation of the left frontal or left parietal cortex, and to characterize the retinotopic profile for any such effects. Moreover, we could now formally compare any such effects upon the visual cortex elicited by stimulation of either left-hemisphere site against the effects when stimulating their right-hemisphere homologues (as initially described in Ruff et al., 2006, 2008), as the same stimulation protocol was employed in the same participants, with only the TMS site being varied. Finally, we also used data acquired for TMS to a vertex control site that should not be expected to affect activity in the visual

cortex, except via the potential nonspecific effects of TMS administration per se (such as the ''clicking'' sound or the scalp sensation associated with TMS pulses). Indeed, TMS to the vertex was found to have no effect on activity in the visual cortex (see also Ruff et al., 2006), which therefore allowed us to directly subtract out any nonspecific TMS effects (auditory activations, etc.) when considering the results for each ''active'' TMS site by itself. For comparison between different ''active'' TMS sites, any nonspecific effects should be subtracted out in any case.

In all experiments, participants had to fixate centrally, with no other task during scanning, to ensure that any remote physiological influences of TMS upon activity in the visual cortex could not possibly be contaminated by TMS-induced changes in behavior. We administered TMS either while subjects passively viewed a blank display, or while they were presented with bilateral moving/changing visual stimuli designed to activate many visual regions (see Figure 1B, C). This was done to allow a test for whether any TMS influences on activity in the visual cortex (as measured via the BOLD signal) might depend on the level of bottom–up activation via visual inputs.

Participants

The same four male, right-handed participants (age = 26–35 years) as in our previous studies (Ruff et al., 2006, 2008) took part in the present experiments. They had normal vision, good health, and no history of neurological or psychiatric illness. All gave written informed consent in accord with local ethics.

TMS Sites

We used the Brainsight Frameless Stereotaxy System (Rogue Research, Montreal, Canada), together with individual T1-weighted anatomical MR images, to determine the scalp coordinates for placing the TMS probe over the different stimulation sites. The same strategies as for our previous studies (Ruff et al., 2006, 2008) were used to determine the individual stimulation sites. The coordinates for left frontal stimulation (over putative human FEF) were determined on the basis of anatomical criteria (Blanke et al., 2000; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000) in conjunction with activations during a 5-min fMRI session of interleaved rest and auditorily paced voluntary saccades in total darkness. This strategy resulted in a chosen cortical surface site for the left FEF with mean Montreal Neurological Institute (MNI) coordinates $x, y, z = -27, -1, 57$ (standard errors: 0.72, 0.53, 2.44), corresponding well with TMS coordinates used in other human FEF studies (e.g., Grosbras, Laird, & Paus, 2005; O'Shea et al., 2004; Muggleton et al., 2003; Ro, Cheifet, Ingle, Shoup, & Rafal, 1999; Paus, 1996). For the left IPS TMS site, we adopted a normalized MNI coordinate ($x, y, z = -36, -48, 45$) based on the mean coordinates of published activation peaks in the IPS during covert shifts of attention and/or eye movement planning and execution (taken

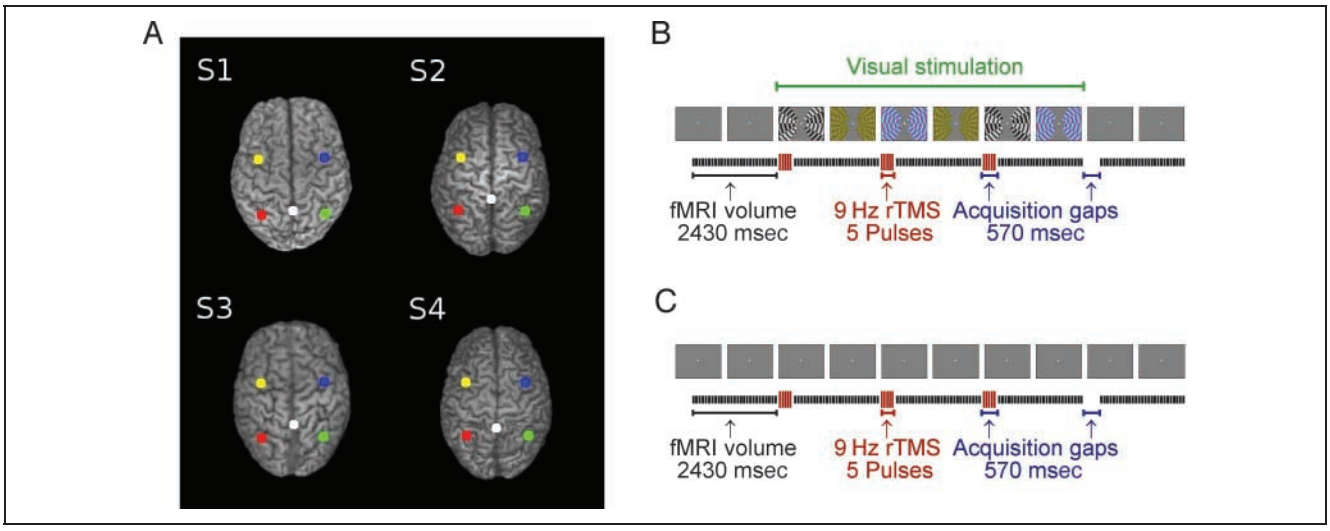

Figure 1. TMS sites in individual participants and experimental design. (A) Three-dimensional images of the individual structural scans of our participants (all brains viewed from above; S1 = Subject 1, etc.). Colored dots mark the position of the five TMS sites studied here, including the two new left-hemisphere sites (yellow for left FEF, red for left IPS) and three sites from previous work by Ruff et al. (2006, 2008; blue for right FEF, green for right IPS, and white for the vertex control site). (B and C) A schematic time course (with time running left to right, and successive rectangles indicating successive screen displays) of a single block of interleaved TMS–fMRI: (B) with visual stimuli on the screen during TMS, or (C) without visual stimuli other than the constant central fixation point on a blank gray screen. For each block, three TMS trains were delivered in the 570-msec gaps between the acquisitions of subsequent image volumes, at one of the four intensities used (see Methods). Seven rest scans were included between successive blocks. Visual stimuli (when present, as in six of the illustration panels for B) remained visible during all three TMS trains and during the acquisition of the three image volumes following the TMS trains.

from Brown et al., 2004; Curtis, Rao, & D'Esposito, 2004; Connolly, Goodale, Menon, & Munoz, 2002; Connolly, Goodale, DeSouza, Menon, & Vilis, 2000; Perry & Zeki, 2000; Corbetta et al., 1998). Perhaps the most important point is that the selection procedure for right and left homologue sites was thus equivalent, allowing for meaningful comparisons between the effects arising in the visual cortex when stimulating these sites.

fMRI Procedures

The experiments described here used the same setup, scanners, and fMRI sequences as our other recent TMS–fMRI studies (Ruff et al., 2006, 2008), to enable the novel direct statistical comparison of the impact of left frontal or parietal TMS against the impact of TMS to comparable right-hemisphere sites, for activity in the visual cortex as assessed with fMRI. A 3-T head scanner (Magnetom Allegra, Siemens Medical, Erlangen, Germany) was used to acquire T1-weighted structural anatomical images and the fMRI data used for retinotopic mapping of visual areas. A 1.5-T whole-body scanner (Magnetom Sonata, Siemens Medical) was used for acquisition of the saccade localizers (with the standard Siemens CP head coil) and of the functional data for the critical TMS sessions. For the TMS sessions, we employed a custom-built visual surface MR coil (Nova Medical, Boston, MA, USA) with maximum sensitivity over the occipital cortices, as the questions we sought to address here all concerned possible activity changes in the visual cortex.

All experimental TMS datasets were acquired with an identical multislice gradient-echo EPI sequence (27 oblique axial slices, 64 × 64 matrix, in-plane resolution: 3 × 3 mm^2, 2.5 mm slice thickness, 1.25 mm spatial gap between adjacent slices, TE = 50 msec, slice TR 90 msec, 2298 Hz/pixel receiver bandwidth, echo spacing = 500 μsec). A 570-msec gap (see Figure 1B, C) was included between the acquisitions of subsequent volumes to allow for enough time to apply TMS pulses within the scanner during this gap, without influencing MR image acquisition. To shift any possible residual Nyquist ghost in the direct vicinity of the TMS probe outside the brain image, 50% oversampling was implemented in the phase encoding direction. For each TMS experiment, 606 image volumes were recorded, lasting 30 min and 18 sec.

TMS Procedures

TMS was employed inside the MR scanner using a Magstim Super Rapid stimulator and custom-built, figure-of-eight, MR-compatible nonferrous coils (from The MAGSTIM Company, Dyfed, UK; same as used in Ruff et al., 2006, 2008). To eliminate potential interference with image acquisition from RF noise generated by the TMS device, the stimulator box was housed in an RF-shielded metal cabinet and connected with the TMS coil through a custom filter box (The MAGSTIM Company) and further ferrite sleeves (Wuerth Elektronik, Waldenburg, Germany). The stimulator was remotely controlled by the same MATLAB script that was also used to deliver the visual stimuli (see below).

Inside the scanner, the participant's head was fixed with a standard vacuum-suction cushion (Siemens Medical). A nonferromagnetic custom holder with several degrees of freedom in each direction was used to firmly position the TMS coil tangentially over the left FEF or left IPS site (see Figure 1A). The initial flow of the induced current was either in posterior–anterior (FEF) or in anterior–posterior (IPS) direction, but biphasic pulses were applied in all experiments. On each trial, three equal-intensity trains of five TMS pulses (at 9 Hz, intensity either at 85%, 70%, 55%, or 40% of stimulator output) were applied in the 570-msec temporal gap between acquisitions of three subsequent image volumes. The maximum stimulation intensity (85%) used during scanning only corresponded to 118% (±14%) of resting motor threshold for our subjects when applied over the motor cortex, due to the custom nonferrous TMS coil used and the resistive properties of the MR-compatible connecting cable. We confirmed by piloting, by visual inspection during the experiment, and by participant report that this TMS protocol did not induce any muscle twitches, as expected given the TMS sites involved. Six stimulation trials were administered for each of the eight conditions (four TMS intensity levels, each with peripheral visual stimulation present or absent) at each TMS site. Our protocol thus contained a total of 48 TMS stimulation blocks (720 pulses in total) per TMS site, complying with published safety limits for repetitive TMS (Wassermann, 1998). Each experiment also contained 12 control trials without any TMS, during which visual stimuli could be present or absent also. All trials were separated by a constant intertrial interval (ITI) of seven image volumes without any stimulation. The order of conditions for each TMS site was randomly determined by the program used to deliver all experimental stimulation. This program was implemented in the MATLAB (The Mathworks, Natick, MA) stimulus presentation toolbox COGENT (www.vislab.ucl.ac.uk/Cogent2000/index.html).

Visual Stimulation and Eye Tracking

On half of the trials, we projected dynamic visual patterns onto a frosted screen (30° × 22° visual angle, gray background, 0.5° × 0.5° central fixation cross always present) mounted at the rear end of the scanner bore. Participants viewed this screen via a mirror system sitting on top of the MR surface coil. As in Ruff et al. (2006, 2008), the stimuli were patterns that spared the fovea and the vertical meridian, that randomly changed form and color every 500 msec, and that randomly moved on

each frame (whole-pattern movement, maximum translation in both horizontal and vertical direction of 0.3° per 16-msec frame). These patterns, when present, were visible on the screen throughout the three TMS trains per trial and the associated consecutive MR image volumes (see Figure 1B). This manipulation of visual stimulation (present or absent) was implemented to assess whether any influences of frontal or parietal TMS upon activity in the visual cortex would depend upon current visual context.

To confirm whether participants kept fixation throughout the experiment, we measured eye position, pupil diameter, and any blinks at 60 Hz during scanning with an ASL 504 remote optics infrared eye tracker (Applied Science Laboratories, Bedford, MA). Eye signals were obtained with the same mirror used for visual stimulus viewing. Raw eye position data were filtered for blinks (continuous losses of pupil signal for more than 80 msec) and transformed to degrees of visual angle before analysis.

Image Processing and Analyses

Data from the left FEF and left IPS experiments underwent exactly the same SPM2 (www.fil.ion.ucl.ac.uk/spm) analyses as the data for the right-hemisphere sites. Functional images were reconstructed off-line, and the first six images of each run were discarded to account for T1 equilibration effects. Images were realigned to the first of the series and corrected for movement-induced image distortions (Andersson, Hutton, Ashburner, Turner, & Friston, 2001). Any slices containing TMS capacitor-induced artifacts (less than 1%) were identified as outlier changes in the slice signal by more than 3 *SD* of the mean slice difference in the time series between consecutive volumes, and were replaced by the mean of the spatially equivalent slices from the previous and the subsequent image volume. For analyses in stereotactic space (which were further complemented by individual retinotopic analyses, see below), images were normalized to the MNI anatomical standard space and spatially smoothed with a three-dimensional 6-mm FWHM Gaussian kernel, in accord with the SPM approach.

Voxelwise effects of each experimental condition per TMS site were estimated by multiple regression of the voxel time series onto a composite model with 10 covariates of interest per session (four TMS stimulation intensities and no TMS, each with and without visual stimulation). These covariates were derived by convolving appropriately placed series of delta functions with the canonical hemodynamic response function employed in SPM2. The model additionally contained one regressor representing eye blinks and another regressor for mean pupil diameter per scan. This multiple regression approach ensured that any variance in brain activity shared by two regressors (e.g., activity that might correlate with both TMS intensity and eye blinks) was not included in our fMRI results (Friston et al., 1995). The model removed low-frequency drifts and short-term temporal autocorrelation of scans by means of a high-pass filter (128 sec cutoff) and an AR(1) process, respectively (Friston et al., 2002). After model estimation, linear contrasts were used to assess and compare the effects associated with the different experimental conditions. Correlations of BOLD with TMS intensity were modeled as the corresponding weighted linear combination of the four covariates representing the different TMS intensities. For all analyses, the statistical threshold was set to $t > 3$ and a cluster threshold of $p < .05$, corrected for multiple comparisons across the image volume. All reported peak voxel coordinates correspond to the MNI space employed in SPM2.

In addition to standard SPM group analyses in stereotactic space, individually defined retinotopic visual areas V1–V4 and area V5/MT+ were analyzed for TMS-induced activity changes. For all these analyses, mean BOLD signal estimates during the different conditions were extracted from the individually defined regions (see below) in the same fashion for each TMS site, and were directly compared by means of repeated measures ANOVAs and subsequent paired *t* tests for planned comparisons. This repeated measures approach was appropriate given our use of the same subjects in each experiment for all conditions. Moreover, although different TMS sites were used in different scanning sessions, we did not just compare overall session effects per se, but rather the effects of specific manipulations within sessions (TMS intensity, crossed with presence and absence of visual stimuli) for the different TMS sites.

Retinotopic areas V1–V4 were determined for each participant individually by a standard retinotopic meridian mapping localizer, consisting of a 5-min fMRI session of subjects viewing flickering checkerboards presented in an alternating fashion either along the horizontal or vertical meridian. The unsmoothed data from this session were modeled voxelwise using a general linear model that included the two meridian conditions. The borders of visual areas V1–V4 (Sereno et al., 1995) were then plotted onto cortical flatmaps derived by segmentation and cortical flattening in MrGray (Wandell, Chial, & Backus, 2000; Teo, Sapiro, & Wandell, 1997). These flatmaps and region definitions were used to inspect the SPM(*t*)s quantifying the correlation of TMS intensity and BOLD signal from the main experiments. For these retinotopic analyses of the impact from each active TMS site, we always directly controlled for any possible nonspecific effects of TMS (e.g., due to the ''click-sound'' or scalp sensation associated with TMS pulses) on early retinotopic visual cortex. This was done by subtracting out the (null) effects of TMS to the vertex control site when characterizing the activation patterns for each of the two new active sites of interest in isolation; or by directly comparing effects for two active TMS sites.

As for our previous studies, which had found systematically different effects of right FEF TMS upon representations of the central versus peripheral visual field in early visual cortex, the V1–V4 data were analyzed for TMS effects in representations of different visual eccentricity. Each area was divided into four different eccentricity ''sectors,'' moving progressively from more to less foveal (see also Ruff et al., 2006, 2008; Schwartz et al., 2005). The correlation of BOLD signal with TMS intensity was quantified as t value in relation to voxelwise noise, and averaged across the voxels contained in each sector. This statistic-based approach ensured that TMS-induced effects could be compared across different eccentricity sectors, and different experiments, without being confounded by voxel- or session-specific noise. Moreover, averaging TMS effects across all voxels for particular eccentricity sectors of the retinotopic cortex (rather than the less conservative strategy of selecting the peak voxels displaying the maximum effects), allowed us to compare effects between sectors, regions, and experiments in a spatially unbiased manner.

Visual area V5/MT+ was defined in each participant by means of a separate 5-min fMRI session with alternating presentations of moving or static starfields. These stimuli spared the fovea by 2° to each side. A voxelwise general linear model with two conditions was applied to the unsmoothed data to determine the cortical region in the lateral occipital cortex maximally driven by moving relative to static starfield stimuli, corresponding to the putative anatomical location of V5/MT+ (see e.g., Rees, Friston, & Koch, 2000; Watson et al., 1993). TMS intensity-dependent effects in this region during the main experiment were then assessed by extracting mean signals per condition (SPM betas scaled for each voxel as percent of the session mean) from spherical regions of interest (V5/MT+ ROIs, 6 mm radius) centered at the individual peak of activations elicited by the motion localizer in this area. We compared the two highest TMS intensities (85% and 70% total output) versus the two lowest (55% and 40% total output) when considering each specific visual area, doing so separately for trials with and without visual stimuli present on the screen.

RESULTS

We compared effects of TMS over the left versus right frontal sites, or left versus right parietal sites, in two complementary sets of analyses. Initially, we used a standard group-analysis approach for each of the four active TMS sites to identify regions in stereotactic space that showed systematic relationships of BOLD with TMS intensity. The particular patterns of influence for left- or right-hemisphere TMS sites upon specific visual areas were then characterized in more detail, and compared directly, by means of individual retinotopic analyses in conjunction with cortical flattening for V1–V4, and via ROI analysis for V5/MT+.

Frontal TMS: Group Analyses in Stereotactic Space

We had previously observed (Ruff et al., 2006) that frontal TMS over the right FEF leads to systematic activity increases in the bilateral cuneus (representing the peripheral visual field), but leads to bilateral activity decreases instead in the occipital poles (representing the central visual field). We now performed the corresponding group analysis for the new left frontal TMS data. This revealed very similar activity decreases in the occipital poles of both hemispheres (Figure 2A) as a function of increasing intensity of TMS administered over the left FEF. The locations of these TMS-elicited activity decreases were virtually identical to those previously found for the right frontal TMS experiment (see lower part of Figure 2 for overlay of the regions found in both experiments). However, we now did not find any region that showed activity *increases* as a function of increasing intensity of TMS over the left FEF, in contrast to the strong activations found for this comparison in the right FEF TMS dataset (see Figure 2B). Finally, the effects of TMS within either frontal TMS experiment were very similar when visual stimuli were present or absent; no regions were found that displayed any interaction of frontal TMS intensity with visual stimulus presence/absence. These apparent similarities (activity decreases for the occipital poles/central visual field; and independence of concurrent visual stimulation) and differences (activity increases for the cuneus regions/peripheral visual field only after right frontal TMS) in the effects of left versus right frontal TMS were confirmed and further specified in the individual retinotopic analyses described below.

Frontal TMS: Individual Analyses of Specific Visual Areas

We further characterized the spatial topography of left versus right frontal TMS effects on specific visual areas by means of individual analyses. To this end, we created flattened representations of each participant's visual cortices, determined the borders of visual areas V1–V4 on these flatmaps by means of standard retinotopy procedures, and divided each of these areas into four eccentricity sectors coding the central through to more peripheral eccentricities in the visual field (see Methods). For each region, we could then derive the inter-subject mean correlation of BOLD with TMS intensity in each of these eccentricity sectors, to directly characterize and compare the spatial topography of effects of left versus right FEF TMS.

Figure 3A shows the effects of TMS to the left FEF (left histogram) or the right FEF (right histogram) on BOLD

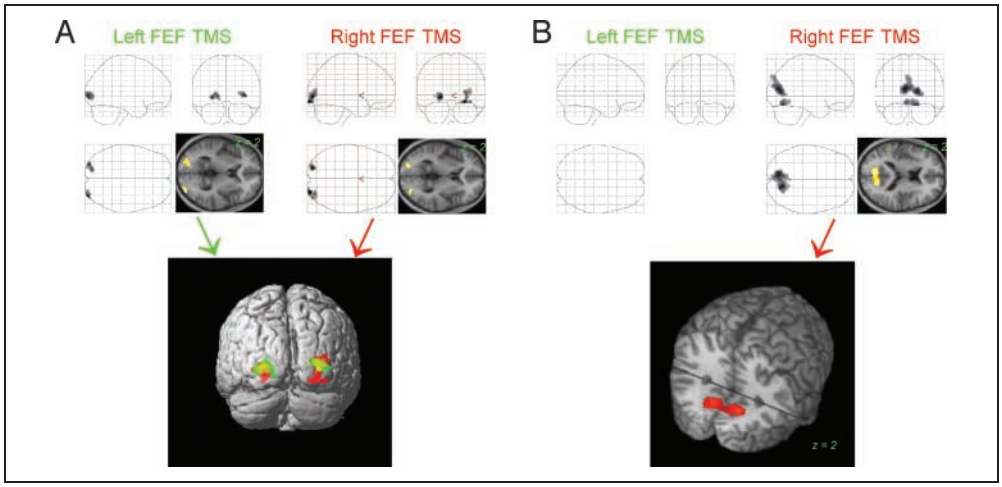

Figure 2. Group analyses of frontal TMS data: Occipital regions displaying activity changes correlating with intensity of TMS over the left or right FEF. (A) All occipital regions that displayed reliable BOLD signal decreases with increased intensity of frontal TMS over the left or right FEF. All upper panels in (A) are SPM(t) images corresponding to the negative correlation of BOLD signal with the intensity of TMS, rendered either on sagittal, coronal, or transverse views of a transparent version (so that no effects are obscured) of the MNI brain template, or onto a transversal slice of the template structural image. The threshold is set to $t = 3$ and a cluster-level $p < .05$, corrected across the brain volume. In the bottom panel, a rendering of these SPM(t)s onto a standard 3-D brain template shows the clear similarity between the effects of left and right frontal TMS: Both lead to bilateral BOLD signal decreases at the occipital poles as TMS intensity increases (shown in green for left frontal TMS, in red for right frontal, and in yellow for overlapping BOLD effects from either frontal TMS site). (B) The outcome when testing instead for BOLD signal increases with increased intensity of frontal TMS over the left or right FEF. Whereas the medial occipital cortex (representing the peripheral visual field) showed such an influence during right frontal TMS over the FEF (shown in the cutaway 3-D rendering on a standard brain template at bottom of B), there were no such effects of corresponding left frontal TMS.

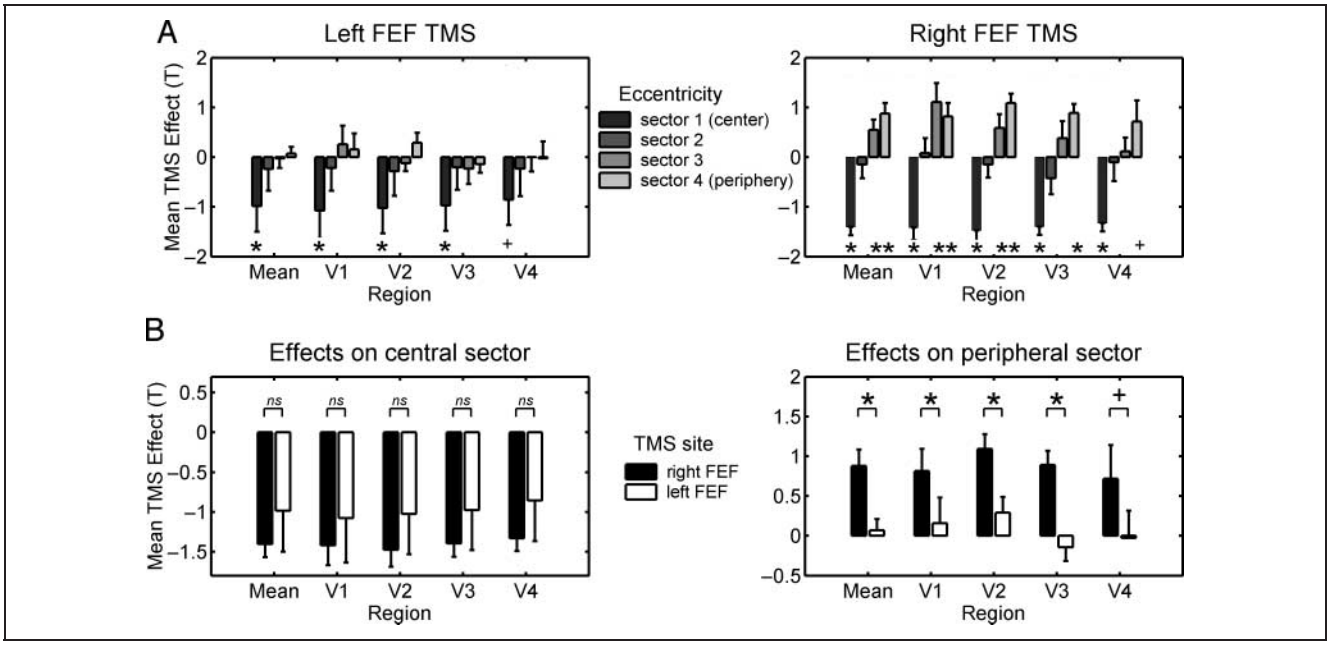

Figure 3. Retinotopic analyses of areas V1–V4: Higher intensity of left or right frontal TMS elicits similar BOLD decreases for the central visual field, but only right frontal TMS leads to BOLD increases for the peripheral visual field. (A) The pattern of effects of TMS to the left or right FEF upon BOLD signal in each of four different eccentricity sectors within visual areas V1–V4. See main text for how the eccentricity sectors were derived, but note that the first along the x-axis for each visual area in A corresponds to the representation of the central visual field, with the next three successive sectors (further to the right along the x-axis, for each visual area) corresponding to increasingly eccentric visual field representations. The correlation of TMS intensity with BOLD (quantified as t value, as in Ruff et al., 2006, 2008) was averaged across flatmaps and voxels within each eccentricity sector of areas V1–V4. These average correlations ($\pm SEM$) are displayed here either averaged across visual areas V1–V4 (''mean''; shown in leftmost group of bars of each histogram in A), or separately for each area V1 through to V4, pooling across the dorsal and ventral cuneus. In all these retinotopic visual areas, increased TMS intensity over the right FEF produced activity increases for the peripheral sectors and activity decreases for the central sector, whereas left FEF TMS only elicited activity decreases for the central sector in all visual areas ($^*p < .05$, $^+p < .1$ in simple t tests). (B) Direct comparisons of the TMS effects of either frontal stimulation site on the most central sector (left histogram) or most peripheral sector (right histogram). These plots confirm for each visual area that the TMS-induced activity decreases in the most central sector did not differ for left versus right frontal TMS (*ns* = not significant), whereas the TMS-induced activity increases in the peripheral sector were consistently stronger during right than left frontal TMS ($^*p < .05$, $^+p < .1$ in paired t tests).

signal in each eccentricity sector (four sectors, going from most central to most peripheral) of visual regions V1–V4, plotted as *t* values to convey the robustness of all effects relative to noise. Increased intensity of either left or right frontal TMS elicited similar activity *decreases* for representations of the central visual field (darkest bars in the histograms of Figure 3A), in good accord with the similar activity decreases that had been observed for the occipital poles in the group stereotactic analyses (cf. Figure 2A). However, strong (and significant) differences in the effects of left versus right FEF TMS were observed for activity changes in peripheral visual field representations: Whereas right frontal TMS led to reliable activity increases in these sectors for all early retinotopic visual areas (see pale bars in right histogram of Figure 3A), no reliable effects on BOLD signal were observed in these sectors for the left frontal TMS data (see left histogram in Figure 3A). Moreover, this was not simply a null result, as the impact of left frontal versus right frontal TMS on peripheral visual field representations for V1–V4 differed significantly between the two TMS sites (see below).

This pattern of some similarities (activity decreases for the central visual field), but also some differences (concerning activity increases in representations of the peripheral visual field), for effects of left versus right frontal TMS was confirmed in direct statistical comparisons. We calculated a 2 (TMS over left vs. right FEF) × 2 (most central vs. most peripheral sector) × 2 (visual stimuli absent vs. present) repeated measures ANOVA on the TMS-intensity effects (correlations of BOLD with TMS intensity, quantified as *t* value), pooled across cortical hemisphere and the dorsal and ventral parts of V1–V4 (there were no reliable differences due to those factors). This analysis showed a significant main effect of eccentricity sector [$F(1, 56) = 35.6, p < .000001$] and a significant interaction of eccentricity sector with stimulation site [$F(1, 56) = 7.41, p < .01$], arising because left or right frontal TMS-intensity effects differed for peripheral but not for central visual field representations (see below). The factor of visual stimulation did not modulate the impact of frontal TMS intensity (all $p > .05$). This confirms the initial findings from the group SPM analyses above, which had also shown that the influences of left and right FEF TMS were each similar during either the presence or absence of concurrent visual input. Note that a similar pattern was found when each retinotopic visual area was considered separately.

Figure 3B displays TMS effects for the most central and most peripheral eccentricity sector in detail for each retinotopic visual area, and marks the significance of planned comparisons between effects of the two frontal stimulation sites (i.e., over the left vs. right FEF, now plotted as white or black bars, respectively). These plots show that in each retinotopic visual area, the activity decreases in the eccentricity sector representing the central visual field (left histogram in Figure 3B) were comparable in magnitude for left or right frontal TMS. By contrast, the activity increases observed in the most peripheral sector, as a consequence of right frontal TMS, were significantly stronger than during left frontal TMS in each visual area (albeit only at trend level for V4; see right histogram in Figure 3B).

Finally, we also conducted ROI analyses to examine BOLD signal in visual area V5/MT+ (see Methods), which we had been found to be unaffected by the intensity of TMS to the right FEF (see Ruff et al., 2008). The new left FEF data similarly showed no significant effect of TMS intensity on BOLD in V5/MT+, neither during the presence nor absence of concurrent visual stimuli.

Parietal TMS: Group Analyses

We recently reported that right parietal TMS (over the IPS) led to activity changes in the occipital visual cortex that differed qualitatively from those due to right frontal TMS (see Ruff et al., 2008). Our new dataset now allowed a direct comparison of the impact of left versus right parietal TMS on BOLD signal in the occipital visual cortex (analogous to the comparison of left vs. right frontal TMS data presented above). These new analyses revealed clear hemispheric differences: Whereas right parietal TMS elicited BOLD signal changes in the visual cortex that depended strongly on the current visual context (i.e., the presence or absence of visual input), the new left parietal TMS data showed no influence of left IPS TMS on the occipital cortex. Importantly, this new finding was not just a null result, as the patterns found in the visual cortex for right versus left parietal TMS were significantly different in direct statistical comparisons.

Specifically, for the right parietal site, TMS-induced activity increases arose in the medial cuneus only in the *absence* of concurrent visual input (see Figure 4A, blue line plots with star), whereas activity decreases due to right parietal TMS were found in the lateral occipital cortex (corresponding to V5/MT+ as confirmed further below), only when the moving visual stimuli were *present* (see Figure 4B, blue line plots with star). In the new left IPS experiment, by contrast, we did not find any region in the recorded image volume that showed systematic activity changes as a function of TMS intensity (see left panels in Figure 4A and B), neither during the absence nor during the presence of the visual stimuli. Likewise, no region was found to display an interaction of left parietal TMS intensity with presence versus absence of visual stimuli.

We confirmed a significant difference in outcome between left versus right parietal TMS, by direct statistical comparisons between the two parietal experiments. For individually defined area V5/MT+ (as determined by a motion localizer; see Methods), we extracted the mean BOLD signals in the different experimental conditions and compared the TMS-intensity effects (two highest TMS intensities minus two lowest; see Methods and also

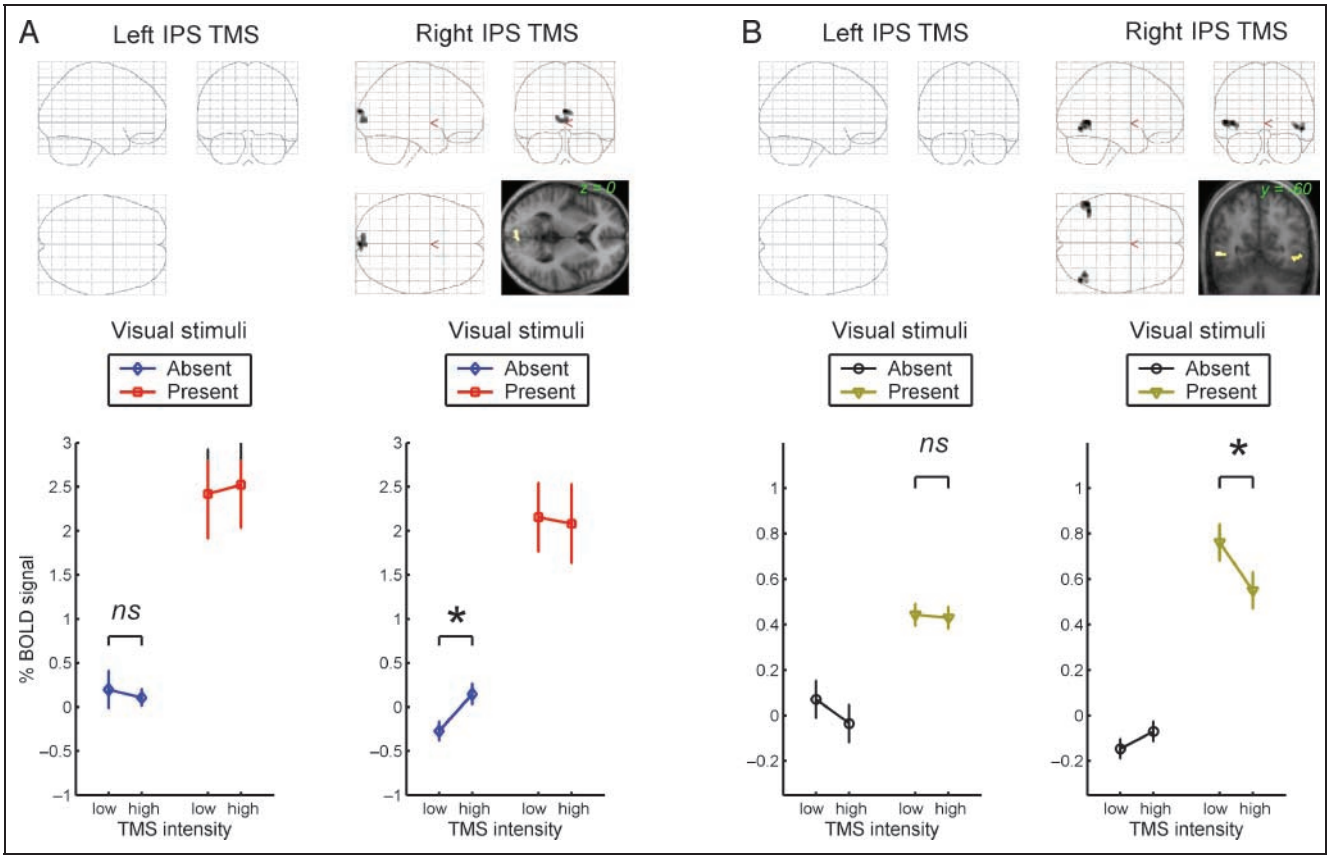

Figure 4. Group analyses of parietal TMS data: Right but not left parietal TMS elicits BOLD changes in the visual cortex that depend on current visual context. (A–B) Two sets of occipital regions where increased intensity of right parietal TMS elicited BOLD effects that depended on visual context (see also Ruff et al., 2007), whereas no such effects were found for left parietal TMS. The images in both panels show SPM(t)s (thresholded at $t > 3$ and $p < .05$, cluster-level corrected across the image volume) quantifying (A) positive correlations of BOLD with parietal TMS intensity, specifically during the absence of visual stimuli; or (B) negative correlations of BOLD with parietal TMS intensity, now during the presence of visual stimuli. Within both (A) and (B), SPMs for the new left parietal TMS experiment are shown on the left, whereas the right parietal TMS data are shown on the right. The line plots displayed at the bottom of (A) show the mean signal intensity ($\pm SEM$) during the different experimental conditions, as extracted from a spherical ROI (6 mm radius) centered in the peak medical cuneus voxel of the SPM(t) for the right parietal TMS data shown above. Note that significant BOLD decreases ($p < .05$ in paired t tests, marked by a star) during the absence of visual stimuli were only found in this medial occipital region for right parietal TMS, but not for left parietal TMS (*ns* = not significant). In both experiments, the medical cuneus was, of course, more active during visual stimulation (red lines) than in its absence (blue lines), but the TMS effect was only found in the absence of visual stimuli, and only for right parietal TMS (see star). The line plots displayed at the bottom of (B) show the mean BOLD signal intensity ($\pm SEM$) during left or right parietal TMS in area V5/MT+, as determined for each subject with an fMRI motion localizer (see Methods, signal is pooled over hemispheres as all effects were symmetric and bilateral). Increased intensity of right parietal TMS led to significant ($p < .05$ in paired t tests, marked by a star) activity decreases in V5/MT+ only when the moving visual stimuli were present (green line in right plot), whereas no such effects were found for left parietal TMS, with this outcome differing significantly between the left and right parietal TMS sites (see main text).

Ruff et al., 2008) in a 2 × 2 repeated measures ANOVA (Left or right parietal TMS × Visual stimulus present or absent). A significant interaction [$F(1, 31) = 8.05$, $p < .01$] arose between these two factors because right parietal TMS elicited activity decreases in V5/MT+ only during the presence of moving visual stimuli, whereas left parietal TMS had no impact. This was confirmed by planned comparisons, which showed significant TMS effects on V5/MT+ due to right parietal TMS only when in the presence of visual stimuli [$t(1, 7) = 2.59, p < .05$], but no effects for left parietal TMS [$t(1, 7) = 0.26, ns$; see Figure 4B, bottom].

Left versus right parietal TMS effects for the early visual cortex (corresponding to the medial cuneus as shown in Figure 4A) were considered further in individual analyses of retinotopic early visual areas, as described below.

Parietal TMS: Retinotopic Analysis

The different impacts of left or right parietal TMS on the medial occipital cortex (see Figure 4A) were further characterized by direct statistical comparisons of the BOLD signal changes in individually mapped retinotopic visual areas V1–V4. As for the corresponding analyses of the frontal TMS data (see above), we extracted the mean TMS effect from each eccentricity sector in each retinotopic visual area (see Figure 5). This revealed that left

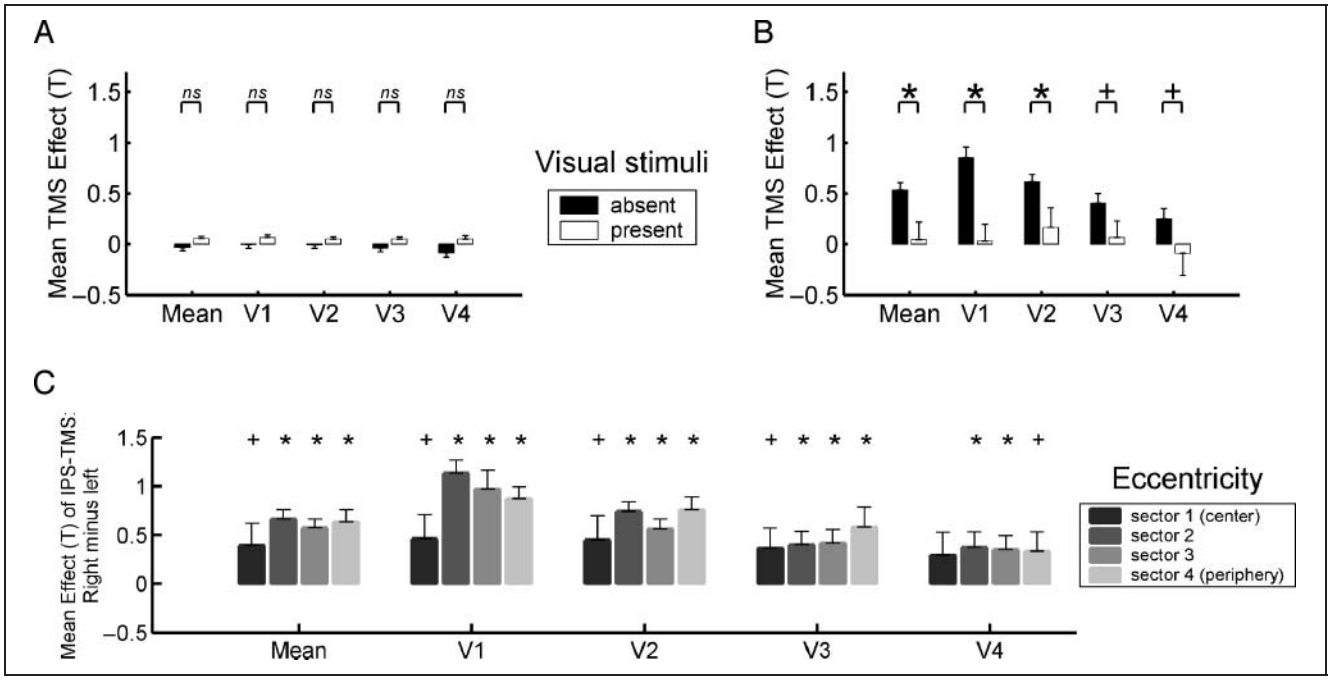

Figure 5. Retinotopic analyses of parietal TMS influences on visual areas V1–V4: Right but not left parietal TMS elicits BOLD increases in V1–V4 during the absence of visual stimuli, for all eccentricity sectors. The upper panels show the mean effects (±*SEM*) of (A) left or (B) right parietal TMS upon BOLD signal in retinotopic visual areas V1–V4, during the presence (white bars) or absence (black bars) of visual input. (A) Increased intensity of left parietal TMS did not lead to activity changes in any of these areas, in neither of the two visual conditions. By contrast, (B) shows that activity increases were found in visual areas V1–V4 for increased intensity of right parietal TMS, but only during the absence of visual stimuli; these activity increases were stronger than during the presence of visual stimuli ($^{*}p < .05$, $^{+}p < .1$ in paired *t* tests). (C) The direct comparison of TMS effects for right minus left parietal TMS, separately for the four eccentricity sectors, either averaged across V1–V4 (''mean,'' at left of histogram) or separately for each area. See main text for how the eccentricity sectors were derived, but note that eccentricity sector number 1 (the first along the *x*-axis for each visual area) corresponds to the representation of the central visual field, with increasing sector numbers (further to the right along the *x*-axis, for each visual area) corresponding to increasingly eccentric visual field representations. The basic findings here are that effects of right parietal TMS on V1–V4 depended on the absence of current visual input, and were similar for different eccentricity sectors; whereas left parietal TMS differed strikingly in having no effect on areas V1–V4, confirming a significant difference between the impact of right versus left parietal TMS on the visual cortex.

parietal TMS had no effect on any retinotopic area (Figure 5A), whereas right parietal TMS affected retinotopic regions only in the absence of visual stimuli (Figure 5B). This difference in impact between right parietal versus left parietal TMS on areas V1–V4 was comparable for all eccentricity sectors (Figure 5C).

These conclusions were confirmed by directly comparing the two parietal experiments in a 2 (left or right parietal TMS) × 2 (most central vs. most peripheral sector) × 2 (visual stimuli present vs. present) repeated measures ANOVA of the TMS-intensity effects (i.e., correlation of BOLD with TMS intensity, quantified by *t* values as also in Ruff et al., 2006, 2008). A significant [$F(1, 56) = 7.38$, $p < .01$] interaction between right versus left parietal TMS and absence versus presence of visual stimulation indicated that right parietal TMS affected the retinotopic visual cortex in the absence but not in the presence of visual input, whereas left parietal TMS had no impact on retinotopic visual areas. This interaction pattern was found in each retinotopic visual area [all $F(1, 56) > 4.56$, all $p < .05$], reflecting activity increases due to right parietal TMS found only during the absence of visual stimuli. We confirmed with pairwise tests that these right parietal TMS-induced increases were indeed reliably larger during the absence than during the presence of visual stimuli (see Figure 5B), and critically also that left parietal TMS did not induce such effects on V1–V4 (all $p > .88$; see Figure 5A).

Figure 5C displays, for every eccentricity sector and visual area, the difference between right-minus-left parietal TMS effects during the absence of visual stimuli. These plots show that, in contrast to the frontal TMS data considered earlier above, the right parietal TMS data did not show any significant effect involving the factor of eccentricity [all $F(1, 56) > 2.81$], and also that right parietal TMS effects were reliably larger than the left parietal TMS effects across all eccentricity sectors. Thus, the data for the new left parietal TMS site do not just reveal a null result, but instead represent a significant difference to the effects of right parietal TMS on the visual cortex.

Eye-data Analyses

Eye position, blinks, and pupil diameter were measured throughout all the fMRI experiments considered here.

It seems implausible that any of these factors could account for our specific fMRI results, given the reliable differences found here for TMS to homologous regions in opposite hemispheres, the differences in the specific retinotopic patterns (in relation to eccentricity sectors), and the dependence versus independence of current visual context for the parietal and frontal TMS effects. We nevertheless took great care to ensure that potential nonspecific effects of TMS upon eye position, blinks, or pupil dilation could not account for the activity changes observed in the visual cortex. As in our previous publications for right-hemisphere TMS (Ruff et al., 2006, 2008), we included blinks and pupil dilations as independent regressors in all of our statistical models of the hemodynamic responses changes elicited by TMS. This ensured that any effect correlating with these eye variables could not contribute to the reported effects. Moreover, we also confirmed with formal statistics that high-intensity TMS, low-intensity TMS, and no-TMS blocks did not differ in mean horizontal and vertical eye position [all $F(2, 237) < 1.46$], nor in the standard deviation of those position signals [all $F(2, 237) < 1.52$], nor in pupil diameter [both $F(2, 237) < 2.8$]. We also confirmed that blinks occurred equally often during trials with high-intensity, low-intensity, or no TMS [$\chi^2(2) = 5.38$].

DISCUSSION

Clinical observations of brain-damaged patients (Becker & Karnath, 2007; Milner & McIntosh, 2005; Mort et al., 2003; Karnath et al., 2002; Mesulam, 1999) and some purely behavioral TMS studies of neurologically healthy people (e.g., Muggleton et al., 2003, 2006; Silvanto et al., 2006; Chambers et al., 2004; O'Shea et al., 2004; Grosbras & Paus, 2002, 2003; Pourtois et al., 2001) have often been taken to suggest that right fronto-parietal areas may play a more predominant role in visual function than comparable left-hemisphere structures (although see Barceló et al., 2000). However, such findings have left it unclear whether any such hemispheric asymmetries may, at least in part, reflect the specific capacity of right-hemisphere fronto-parietal structures to exert remote influences upon the visual cortex, rather than solely reflecting local processing within frontal–parietal areas themselves. Moreover, standard fMRI studies of visual attention have not always agreed on whether the putative fronto-parietal ''attention network'' is strongly right-lateralized in humans, or might be essentially (or partially) bilateral/symmetric, as often suspected for non-human primates (e.g., see Serences & Yantis, 2006; Driver, Eimer, et al., 2004; Driver, Vuilleumier, et al., 2004; Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000, for reviews). In any case, neuroimaging studies, or purely behavioral patient studies, on their own typically cannot identify causal influences between brain areas, which was the central issue considered here when asking whether the impact of right frontal or parietal TMS upon activity in the visual cortex may differ qualitatively from that for comparable left frontal or parietal TMS.

To address this directly, we used concurrent TMS–fMRI to assess with direct statistical comparisons how applying TMS to the left frontal or parietal cortex may differ from effects of corresponding right TMS, in terms of the impact on BOLD activity in human visual areas. We observed marked and statistically significant differences in these influences, indicating that right-hemisphere fronto-parietal areas may play special roles in the network that can modulate the visual cortex. Our data may thus provide a new possible explanation, in terms of remote physiological effects on the visual cortex, for the frequent finding that performance in perceptual tasks is more often affected by TMS to the right (rather than left) fronto-parietal cortex in humans (e.g., Muggleton et al., 2003, 2006; Silvanto et al., 2006; Chambers et al., 2004; O'Shea et al., 2004; Grosbras & Paus, 2002, 2003; Pourtois et al., 2001).

Although increased intensity of TMS over both the left and right frontal cortex elicited strikingly similar activity decreases for *central* visual field representations in V1–V4, only right frontal TMS led to strong BOLD increases for *peripheral* field representations in these regions. This suggests right-hemisphere predominance for frontal influences upon (bilateral) visual cortex representations of the periphery (cf. Mesulam, 1999, for original clinical proposals, based on brain-damaged patients, that some right-hemisphere structures might deal with both sides of space). For the parietal TMS sites, we found even clearer hemispheric differences. Left parietal TMS did not affect BOLD signal in any area of the occipital visual cortex, in contrast to right parietal TMS, which led to BOLD signal changes in V1–V4 and V5/MT+, which were strongly dependent on current visual context (and thus, quite unlike the frontal TMS effects). All these differences in the effects of right- versus left-hemisphere TMS were significant in direct statistical comparisons, providing new causal evidence that right-hemisphere frontal and parietal regions of the human brain can influence activity in the occipital visual cortex in a more pronounced and distinct fashion than homologous left-hemisphere fronto-parietal regions.

The only significant effect of left-hemisphere TMS on the occipital cortex found here consisted of BOLD signal decreases for representations of the central visual field in areas V1–V4 during left frontal stimulation. These particular effects were remarkably similar for both left- and right-frontal TMS, in terms of their spatial extent and magnitude (see Figure 2A). Moreover, all effects of TMS at both these frontal sites applied regardless of the presence versus absence of visual input. This latter finding supports the general notion that frontal influences on processing in the visual cortex may apply in a ''top–down'' fashion (e.g., see Buschman & Miller, 2007, for a recent example) that can operate regardless of

current ''bottom–up'' visual input. But we also found clear hemispheric differences in the effects of frontal TMS on the visual cortex. Only right frontal TMS led to BOLD increases for more peripheral visual field representations in V1–V4 (see Figures 2B and 3), whereas left frontal TMS did not. From a functional point of view, this dissociation of common BOLD decreases (for central visual field) and distinct BOLD increases (for peripheral field only with right frontal TMS) might indicate possible functional specialization of the right frontal cortex for enhancing processing of the peripheral visual field. This might potentially relate to the putative role of the frontal cortex in controlling covert spatial attention to the periphery (e.g., Juan, Shorter-Jacobi, & Schall, 2004; Tehovnik et al., 2000; Mesulam, 1999), and our findings clearly suggest some right-hemisphere dominance for such functional contributions in humans.

From an anatomical perspective, our findings suggest that separable neural tracts may link the human frontal cortex with occipital representations of the central versus the more peripheral visual field. Anatomical separation of FEF–occipital connections by visual eccentricity (central vs. more peripheral) has already been suggested by anatomical tracing studies in the macaque brain (Bullier, Schall, & Morel, 1996; Schall, Morel, King, & Bullier, 1995; Blatt, Andersen, & Stoner, 1990). However, to our knowledge, no study to date has systematically examined possible differences between the anatomical or functional connectivity of the FEFs in the two different cortical hemispheres, neither in humans nor in monkeys. In the monkey brain, FEFs in either hemisphere are generally considered to be symmetric homologues, each with a primarily contralateral preference for visual stimuli (''receptive field'') and for eye movements (''motor fields'') (e.g., Wardak et al., 2006; Tehovnik et al., 2000; Schall & Thompson, 1999). Some contralaterality has also now been suggested for human FEF with fMRI (e.g., Serences & Yantis, 2007; Hagler & Sereno, 2006). Nevertheless, this contralaterality may be relative rather than absolute in humans. Moreover, such studies have, to date, concentrated on activity profiles just within the FEF, whereas here we were concerned instead with causal influences of stimulating the frontal cortex (with TMS) upon activity in the remote but potentially interconnected visual cortex.

Our new findings here provide the first evidence that ''effective connectivity'' of the human left and right frontal cortex with the occipital visual cortex might be similar for representations of the central visual field, yet show right-hemisphere dominance for the more peripheral visual field. Whether this may relate to different anatomical layout and connectivity of the left versus right frontal cortex might be examined in future studies, such as perhaps with diffusion tensor imaging in humans or anatomical tracing techniques in monkeys. For the experiments described here, we had used a surface MR coil centered over the occipital cortex, which allowed us to characterize and compare TMS effects on the retinotopic visual cortex with high sensitivity, but conversely did not record signal from more anterior regions.

It is important to stress, however, that the TMS effects on the visual cortex described here are unlikely to just reflect fixed effects of monosynaptic anatomical connections of the stimulated sites with the visual cortex. For instance, the finding that BOLD changes due to unilateral frontal stimulation arose in the visual cortex bilaterally, and even as early as area V1, suggests the involvement of polysynaptic pathways via intervening cortical or subcortical brain regions (for more extensive discussion, see Ruff et al., 2006, 2008). Moreover, the visual-context-dependence of effects for right-parietal TMS, as described below, suggests that remote effects of TMS may not reflect only fixed anatomical connections, but may rather indicate *functional coupling* between areas that can change with current context, that is, with the functional state of the neuronal circuitry at the time when TMS is applied (see also Bestmann et al., 2007; Massimini et al., 2005; Friston, 2002; Munchau, Bloem, Irlbacher, Trimble, & Rothwell, 2002; McIntosh, 2000).

Our results for TMS to the parietal sites revealed even more striking evidence that right-hemisphere TMS can result in influences upon the visual cortex that comparable left-hemisphere TMS does not produce. Right parietal TMS elicited strong BOLD increases in areas V1–V4 when no visual stimuli were presented, so that the visual cortex was not activated by external input. When visual stimuli were present, by contrast, right IPS TMS specifically affected activity only in visual area V5/MT+, leading to strong decreases in BOLD response to the moving visual stimuli in this region. This change of ''effective connectivity'' between right parietal cortex and areas in the visual cortex, as a function of visual context, may fit the emerging view that neural signals in parietal regions may be more visually driven than those in frontal areas (e.g., Buschman & Miller, 2007), and may possibly relate to flexible, context-dependent coding of the environment (e.g., Wardak et al., 2006; Macaluso & Driver, 2005; Shulman et al., 2003; Culham, Cavanagh, & Kanwisher, 2001; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). Context-dependence of effective connectivity between the right IPS and visual areas might explain why right parietal TMS affected activity in V5/MT+ only in the presence of moving visual stimuli and, by the same token, why functional connections between the right parietal and retinotopic visual cortex (V1–V4) here appeared less responsive to any TMS-driven ''feedback'' influences when TMS was applied in the presence of strong driving visual input, which may have dominated connections between visual cortex and IPS in a ''feedforward'' manner. Future studies might test this conjecture in more detail; for instance, by examining how varying the strength (contrast) of concurrent visual stimulation may affect the modulatory influence of right parietal TMS upon activity in the early visual cortex.

The new data presented here now show that left parietal TMS had drastically different effects, as it did not affect BOLD signal in any visual cortical area, in either visual context (i.e., with or without visual stimuli). Moreover, this was more than just an uninformative null outcome, as the outcome for left parietal TMS differed significantly from that for right parietal TMS. This pattern of marked right-hemisphere dominance for the effects of parietal TMS seems to accord well with clinical observations because deficits such as neglect or extinction are most often reported after lesions of right-hemisphere brain areas in and around the parietal cortex and the IPS, whereas lesions of corresponding parietal regions in the left hemisphere rarely have such effects (Becker & Karnath, 2007; Milner & McIntosh, 2005; Mort et al., 2003; Karnath et al., 2002; Mesulam, 1999). Our findings provide a possible new interpretation of such clinical lesion data, namely, that the marked effects of lesions to right-hemisphere regions of the human parietal cortex may relate to the specific capacity of these regions for functional influences upon the visual cortex. This interpretation could also fit with the fact that some of the clinical sequelae of right parietal damage (e.g., extinction) likewise depend on current visual context (see e.g., Driver, Vuilleumier, et al., 2004; Marzi et al., 2001; Vuilleumier & Rafal, 2000; Mesulam, 1999), as established also for the right parietal TMS effects upon the visual cortex here.

Our new TMS–fMRI findings here may also shed new light on the possible neural mechanisms underlying purely behavioral TMS effects. Several behavioral TMS studies have reported more marked impacts of right- than left-hemisphere frontal or parietal TMS upon visual performance (e.g., Muggleton et al., 2003, 2006; Chambers et al., 2004; O'Shea et al., 2004; Grosbras & Paus, 2002, 2003; Pourtois et al., 2001). But it has so far remained unclear whether such behavioral TMS effects reflect hemispheric differences only in the local function of the stimulated cortical sites, or instead, in their functional interactions with the remote visual cortex. Our new results here provide direct evidence that the visual cortex itself can be more strongly affected when frontal or parietal TMS is administered over the right rather than over the left hemisphere. Such remote influences upon the visual cortex may plausibly underlie some of the marked behavioral effects of right-hemisphere frontal/parietal TMS on performance on visual tasks. This point may also be noteworthy from a purely methodological perspective, as our findings imply that TMS effects on behavior may not solely reflect influences on neural processing directly under the stimulation coil, but also the impact upon other areas in the network of remote but interconnected brain regions participating in a given cognitive function (see also Bestmann, Ruff, Driver, & Blankenburg, 2008; Sack et al., 2007).

In contrast to lesion and TMS investigations in humans, studies in nonhuman primates have, to date, typically not reported (but also rarely sought) hemispheric differences for the perceptual effects of interventions such as lesions, microstimulation, cooling, or chemical inactivation of frontal or parietal brain areas (e.g., Wardak et al., 2004, 2006; Moore & Fallah, 2004). Hemispheric differences in effects of TMS on perceptual behavior, and for remote impacts upon visual cortex as described here, may reflect some aspects of hemispheric specialization that are potentially unique to the human brain (Sun & Walsh, 2006; Davidson & Hugdahl, 1995; Hellige, 1990). Such right-hemisphere lateralization of perceptual control might complement, or even relate in an evolutionary sense, to other hemispheric specializations of the human brain, such as typical left-hemisphere dominance for language processing (e.g., Josse & Tzourio-Mazoyer, 2004). In future work with the new approach developed here, it might now become possible to study with concurrent TMS–fMRI whether regions related to, say, language processing might also show hemispheric differences in terms of their functional connectivity with remote but interconnected brain areas, perhaps with left-hemisphere predominance for remote effects of TMS in a language context.

In conclusion, we found that TMS to right-hemisphere frontal and parietal regions of the human brain could have distinct influences on BOLD signal in visual areas V1–V4 and V5/MT+, which were absent (and significantly different) during TMS over the corresponding left-hemisphere sites. These data directly confirm right-hemisphere predominance for fronto-parietal causal influences upon processing in the human visual cortex, which may, in turn, relate to the stronger perceptual–attentional disruptions typically found after lesions or TMS interventions concerning right-hemisphere human fronto-parietal regions. More generally, our results illustrate how concurrent TMS–fMRI can provide a new approach to the long-standing question of functional lateralization in the human brain, now in relation to causal interactions between remote but interconnected brain regions.

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REFERENCES

Andersson, J. L., Hutton, C., Ashburner, J., Turner, R., & Friston, K. (2001). Modeling geometric deformations in EPI time series. *Neuroimage, 13,* 903–919.

Armstrong, K. M., & Moore, T. (2007). Rapid enhancement of visual cortical response discriminability by microstimulation

of the frontal eye field. *Proceedings of the National Academy of Sciences, U.S.A, 104,* 9499–9504.
Barceló, F., Suwazono, S., & Knight, R. T. (2000). Prefrontal modulation of visual processing in humans. *Nature Neuroscience, 3,* 399–403.
Baudewig, J., Siebner, H. R., Bestmann, S., Tergau, F., Tings, T., Paulus, W., et al. (2001). Functional MRI of cortical activations induced by transcranial magnetic stimulation (TMS). *NeuroReport, 12,* 3543–3548.
Becker, E., & Karnath, H. O. (2007). Incidence of visual extinction after left versus right hemisphere stroke. *Stroke, 38,* 3172–3174.
Bestmann, S., Ruff, C. C., Driver, J., & Blankenburg, F. (2008). Concurrent TMS and functional magnetic resonance imaging: Methods and current advances. In E. Wassermann, C. Epstein, U. Ziemann, V. Walsh, T. Paus, & S. Lisanby (Eds.), *Oxford handbook of transcranial stimulation* (pp. 569–592). Oxford: Oxford University Press.
Bestmann, S., Swayne, O., Blankenburg, F., Ruff, C. C., Haggard, P., Weiskopf, N., et al. (2007). Dorsal premotor cortex exerts state-dependent causal influences on activity in contralateral primary motor and dorsal premotor cortex. *Cerebral Cortex, 26,* 7452–7459.
Blanke, O., Spinelli, L., Thut, G., Michel, C. M., Perrig, S., Landis, T., et al. (2000). Location of the human frontal eye field as defined by electrical cortical stimulation: Anatomical, functional and electrophysiological characteristics. *NeuroReport, 11,* 1907–1913.
Blatt, G. J., Andersen, R. A., & Stoner, G. R. (1990). Visual receptive field organization and cortico-cortical connections of the lateral intraparietal area (area LIP) in the macaque. *Journal of Comparative Neurology, 299,* 421–445.
Bohning, D. E., Shastri, A., McConnell, K. A., Nahas, Z., Lorberbaum, J. P., Roberts, D. R., et al. (1999). A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. *Biological Psychiatry, 45,* 385–394.
Brown, M. R., DeSouza, J. F., Goltz, H. C., Ford, K., Menon, R. S., Goodale, M. A., et al. (2004). Comparison of memory- and visually guided saccades using event-related fMRI. *Journal of Neurophysiology, 91,* 873–889.
Bullier, J., Schall, J. D., & Morel, A. (1996). Functional streams in occipito-frontal connections in the monkey. *Behavioral Brain Research, 76,* 89–97.
Buschman, T. J., & Miller, E. K. (2007). Top–down versus bottom–up control of attention in the prefrontal and posterior parietal cortices. *Science, 315,* 1860–1862.
Chambers, C. D., Payne, J. M., Stokes, M. G., & Mattingley, J. B. (2004). Fast and slow parietal pathways mediate spatial attention. *Nature Neuroscience, 7,* 217–218.
Connolly, J. D., Goodale, M. A., DeSouza, J. F., Menon, R. S., & Vilis, T. (2000). A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing. *Journal of Neurophysiology, 84,* 1645–1655.
Connolly, J. D., Goodale, M. A., Menon, R. S., & Munoz, D. P. (2002). Human fMRI evidence for the neural correlates of preparatory set. *Nature Neuroscience, 5,* 1345–1352.
Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., et al. (1998). A common network of functional areas for attention and eye movements. *Neuron, 21,* 761–773.
Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3,* 201–215.
Culham, J. C., Cavanagh, P., & Kanwisher, N. G. (2001). Attention response functions: Characterizing brain areas using fMRI activation during parametric variations of attentional load. *Neuron, 32,* 737–745.
Curtis, C. E., Rao, V. Y., & D'Esposito, M. (2004). Maintenance of spatial and motor codes during oculomotor delayed response tasks. *Journal of Neuroscience, 24,* 3944–3952.
Davidson, R. A., & Hugdahl, K. (1995). *Brain asymmetry*. Cambridge: MIT Press.
Deco, G., & Zihl, J. (2004). A biased competition based neurodynamical model of visual neglect. *Medical Engineering Physics, 26,* 733–743.
Driver, J., Eimer, M., Macaluso, E., & van Velzen, J. (2004). The neurobiology of human spatial attention. In N. Kanwisher & J. Duncan (Eds.), *Functional neuroimaging of visual cognition: Attention and performance XX* (pp. 267–300). Oxford: Oxford University Press.
Driver, J., & Mattingley, J. B. (1998). Parietal neglect and visual awareness. *Nature Neuroscience, 1,* 17–22.
Driver, J., Vuilleumier, P., & Husain, M. (2004). Spatial neglect and extinction. In M. J. Gazzaniga (Ed.), *The new cognitive neurosciences* (pp. 589–606). Cambridge, MA: MIT Press.
Duncan, J., Humphreys, G., & Ward, R. (1997). Competitive brain activity in visual attention. *Current Opinion in Neurobiology, 7,* 255–261.
Friston, K. (2002). Beyond phrenology: What can neuroimaging tell us about distributed circuitry? *Annual Review of Neuroscience, 25,* 221–250.
Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., & Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping, 2,* 189–210.
Friston, K. J., Penny, W., Phillips, C., Kiebel, S., Hinton, G., & Ashburner, J. (2002). Classical and Bayesian inference in neuroimaging: Theory. *Neuroimage, 16,* 465–483.
Frith, C. (2001). A framework for studying the neural basis of attention. *Neuropsychologia, 39,* 1367–1371.
Grosbras, M. H., Laird, A. R., & Paus, T. (2005). Cortical regions involved in eye movements, shifts of attention, and gaze perception. *Human Brain Mapping, 25,* 140–154.
Grosbras, M. H., & Paus, T. (2002). Transcranial magnetic stimulation of the human frontal eye field: Effects on visual perception and attention. *Journal of Cognitive Neuroscience, 14,* 1109–1120.
Grosbras, M. H., & Paus, T. (2003). Transcranial magnetic stimulation of the human frontal eye field facilitates visual awareness. *European Journal of Neuroscience, 18,* 3121–3126.
Hagler, D. J., Jr., & Sereno, M. I. (2006). Spatial maps in frontal and prefrontal cortex. *Neuroimage, 29,* 567–577.
Hellige, J. B. (1990). Hemispheric asymmetry. *Annual Review of Psychology, 41,* 55–80.
Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top–down attentional control. *Nature Neuroscience, 3,* 284–291.
Josse, G., & Tzourio-Mazoyer, N. (2004). Hemispheric specialization for language. *Brain Research, Brain Research Review, 44,* 1–12.
Juan, C. H., Shorter-Jacobi, S. M., & Schall, J. D. (2004). Dissociation of spatial attention and saccade preparation. *Proceedings of the National Academy of Sciences, U.S.A., 101,* 15541–15544.
Karnath, H.-O., Milner, A. D., & Vallar, G. (2002). *The cognitive and neural bases of spatial neglect*. Oxford: Oxford University Press.
Kastner, S., Pinsk, M. A., De Weerd, P., Desimone, R., & Ungerleider, L. G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron, 22,* 751–761.
Kastner, S., & Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annual Review of Neuroscience, 23,* 315–341.

Macaluso, E., & Driver, J. (2005). Multisensory spatial interactions: A window onto functional integration in the human brain. *Trends in Neurosciences, 28,* 264–271.
Marzi, C. A., Girelli, M., Miniussi, C., Smania, N., & Maravita, A. (2000). Electrophysiological correlates of conscious vision: Evidence from unilateral extinction. *Journal of Cognitive Neuroscience, 12,* 869–877.
Marzi, C. A., Girelli, M., Natale, E., & Miniussi, C. (2001). What exactly is extinguished in unilateral visual extinction? Neurophysiological evidence. *Neuropsychologia, 39,* 1354–1366.
Massimini, M., Ferrarelli, F., Huber, R., Esser, S. K., Singh, H., & Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. *Science, 309,* 2228–2232.
McIntosh, A. R. (2000). Towards a network theory of cognition. *Neural Networks, 13,* 861–870.
Mesulam, M. M. (1999). Spatial attention and neglect: Parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences, 354,* 1325–1346.
Miller, B. T., & D'Esposito, M. (2005). Searching for ''the top'' in top–down control. *Neuron, 48,* 535–538.
Miller, E. K. (2000). The neural basis of the top–down control of visual attention in the prefrontal cortex. In S. Monsell & J. Driver (Eds.), *Control of cognitive processes: Attention and performance XVIII* (pp. 511–534). Cambridge, MA: MIT Press.
Milner, A. D., & McIntosh, R. D. (2005). The neurological basis of visual neglect. *Current Opinion in Neurology, 18,* 748–753.
Moore, T., & Armstrong, K. M. (2003). Selective gating of visual signals by microstimulation of frontal cortex. *Nature, 421,* 370–373.
Moore, T., & Fallah, M. (2004). Microstimulation of the frontal eye field and its effects on covert spatial attention. *Journal of Neurophysiology, 91,* 152–162.
Mort, D. J., Malhotra, P., Mannan, S. K., Rorden, C., Pambakian, A., Kennard, C., et al. (2003). The anatomy of visual neglect. *Brain, 126,* 1986–1997.
Muggleton, N. G., Juan, C. H., Cowey, A., & Walsh, V. (2003). Human frontal eye fields and visual search. *Journal of Neurophysiology, 89,* 3340–3343.
Muggleton, N. G., Postma, P., Moutsopoulou, K., Nimmo-Smith, I., Marcel, A., & Walsh, V. (2006). TMS over right posterior parietal cortex induces neglect in a scene-based frame of reference. *Neuropsychologia, 44,* 1222–1229.
Munchau, A., Bloem, B. R., Irlbacher, K., Trimble, M. R., & Rothwell, J. C. (2002). Functional connectivity of human premotor and motor cortex explored with repetitive transcranial magnetic stimulation. *Journal of Neuroscience, 22,* 554–561.
O'Shea, J., Muggleton, N. G., Cowey, A., & Walsh, V. (2004). Timing of target discrimination in human frontal eye fields. *Journal of Cognitive Neuroscience, 16,* 1060–1067.
Paus, T. (1996). Location and function of the human frontal eye-field: A selective review. *Neuropsychologia, 34,* 475–483.
Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., & Evans, A. C. (1997). Transcranial magnetic stimulation during positron emission tomography: A new method for studying connectivity of the human cerebral cortex. *Journal of Neuroscience, 17,* 3178–3184.
Perry, R. J., & Zeki, S. (2000). The neurology of saccades and covert shifts in spatial attention: An event-related fMRI study. *Brain, 123,* 2273–2288.
Pourtois, G., Vandermeeren, Y., Olivier, E., & de Gelder, B. (2001). Event-related TMS over the right posterior parietal cortex induces ipsilateral visuo-spatial interference. *NeuroReport, 12,* 2369–2374.
Rees, G., Friston, K., & Koch, C. (2000). A direct quantitative relationship between the functional properties of human and macaque V5. *Nature Neuroscience, 3,* 716–723.
Ro, T., Cheifet, S., Ingle, H., Shoup, R., & Rafal, R. (1999). Localization of the human frontal eye fields and motor hand area with transcranial magnetic stimulation and magnetic resonance imaging. *Neuropsychologia, 37,* 225–231.
Ruff, C. C., Bestmann, S., Blankenburg, F., Bjoertomt, O., Josephs, O., Weiskopf, N., et al. (2008). Distinct causal influences of parietal versus frontal areas on human visual cortex: Evidence from concurrent TMS fMRI. *Cerebral Cortex, 18,* 817–827.
Ruff, C. C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Freeman, E., Haynes, J. D., et al. (2006). Concurrent TMS–fMRI and psychophysics reveal frontal influences on human retinotopic visual cortex. *Current Biology, 16,* 1479–1488.
Ruff, C. C., & Driver, J. (2006). Attentional preparation for a lateralized visual distractor: Behavioral and fMRI evidence. *Journal of Cognitive Neuroscience, 18,* 522–538.
Sack, A. T., Kohler, A., Bestmann, S., Linden, D. E., Dechent, P., Goebel, R., et al. (2007). Imaging the brain activity changes underlying impaired visuospatial judgments: Simultaneous fMRI, TMS, and behavioral studies. *Cerebral Cortex, 17,* 2841–2852.
Schall, J. D., Morel, A., King, D. J., & Bullier, J. (1995). Topography of visual cortex connections with frontal eye field in macaque: Convergence and segregation of processing streams. *Journal of Neuroscience, 15,* 4464–4487.
Schall, J. D., & Thompson, K. G. (1999). Neural selection and control of visually guided eye movements. *Annual Review of Neuroscience, 22,* 241–259.
Schwartz, S., Vuilleumier, P., Hutton, C., Maravita, A., Dolan, R. J., & Driver, J. (2005). Attentional load and sensory competition in human vision: Modulation of fMRI responses by load at fixation during task-irrelevant stimulation in the peripheral visual field. *Cerebral Cortex, 15,* 770–786.
Serences, J. T., & Yantis, S. (2006). Selective visual attention and perceptual coherence. *Trends in Cognitive Sciences, 10,* 38–45.
Serences, J. T., & Yantis, S. (2007). Spatially selective representations of voluntary and stimulus-driven attentional priority in human occipital, parietal, and frontal cortex. *Cerebral Cortex, 17,* 284–293.
Sereno, M. I., Dale, A. M., Reppas, J. B., Kwong, K. K., Belliveau, J. W., Brady, T. J., et al. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science, 268,* 889–893.
Shastri, A., George, M. S., & Bohning, D. E. (1999). Performance of a system for interleaving transcranial magnetic stimulation with steady-state magnetic resonance imaging. *Electroencephalography and Clinical Neurophysiology, 51,* 55–64.
Shulman, G. L., McAvoy, M. P., Cowan, M. C., Astafiev, S. V., Tansy, A. P., d'Avossa, G., et al. (2003). Quantitative analysis of attention and detection signals during visual search. *Journal of Neurophysiology, 90,* 3384–3397.
Silvanto, J., Lavie, N., & Walsh, V. (2006). Stimulation of human frontal eye fields modulates sensitivity of extrastriate visual cortex. *Journal of Neurophysiology, 96,* 941–945.

Sun, T., & Walsh, C. A. (2006). Molecular approaches to brain asymmetry and handedness. *Nature Reviews Neuroscience, 7,* 655–662.
Taylor, P. C., Nobre, A. C., & Rushworth, M. F. (2007). FEF TMS affects visual cortical activity. *Cerebral Cortex, 17,* 391–399.
Tehovnik, E. J., Sommer, M. A., Chou, I. H., Slocum, W. M., & Schiller, P. H. (2000). Eye fields in the frontal lobes of primates. *Brain Research, Brain Research Reviews, 32,* 413–448.
Teo, P. C., Sapiro, G., & Wandell, B. A. (1997). Creating connected representations of cortical gray matter for functional MRI visualization. *IEEE Transactions in Medical Imaging, 16,* 852–863.
Vuilleumier, P. O., & Rafal, R. D. (2000). A systematic study of visual extinction. Between- and within-field deficits of attention in hemispatial neglect. *Brain, 123,* 1263–1279.
Wandell, B. A., Chial, S., & Backus, B. T. (2000). Visualization and measurement of the cortical surface. *Journal of Cognitive Neuroscience, 12,* 739–752.
Wardak, C., Ibos, G., Duhamel, J. R., & Olivier, E. (2006). Contribution of the monkey frontal eye field to covert visual attention. *Journal of Neuroscience, 26,* 4228–4235.
Wardak, C., Olivier, E., & Duhamel, J. R. (2004). A deficit in covert attention after parietal cortex inactivation in the monkey. *Neuron, 42,* 501–508.
Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology, 108,* 1–16.
Watson, J. D., Myers, R., Frackowiak, R. S., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., et al. (1993). Area V5 of the human brain: Evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cerebral Cortex, 3,* 79–94.
Winkowski, D. E., & Knudsen, E. I. (2007). Top–down control of multimodal sensitivity in the barn owl optic tectum. *Journal of Neuroscience, 27,* 13279–13291.