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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 right or left fronto-parietal cortex on activity (BOLD signal) in 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 (versus 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 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 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 human frontal and parietal cortex shows right-hemisphere specialization for causal influences on visual cortex.

Keywords

TMS; fMRI; attention; top-down; neglect

It is increasingly recognized that visual processing within 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 (Corbetta & Shulman, 2002; Driver et al., 2004; Duncan et al., 1997; Frith, 2001; Hopfinger et al., 2000; Miller, 2000; Kastner & Ungerleider, 2000; Miller & D’Esposito, 2005; Ruff & Driver 2006; Serences & Yantis, 2006). This might potentially explain some clinical phenomena in humans, whereby lesions in frontal and/or parietal areas, well beyond classical ‘visual’ cortex, can lead to putatively attentional deficits that affect visual abilities, such as neglect or extinction (Driver & Mattingley, 1998; Mesulam, 1999; Vuilleumier & Rafal, 2000; Karnath et al., 2002; Mort et al., 2003; Milner & McIntosh, 2005). Such clinical phenomena are typically more common and pronounced

after right- than left-hemisphere damage. This has been taken to suggest that right frontal and parietal cortex might normally play special roles in influencing activity in visual cortex for humans (e.g., see Mesulam, 1999; Marzi et al., 2000; Marzi et al., 2001; Deco & Zihl, 2004, but see also Barcelo, 2000), that may differ from any influences from 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 Corbetta & Shulman, 2002; Driver et al., 2004; Kastner & Ungerleider, 2000; Serences & Yantis, 2006, for reviews), standard neuroimaging studies are not sufficient on their own to address hemispheric differences in truly causal impacts upon visual cortex. Conversely, while 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 neuroimaging in humans, 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 Moore and colleagues (Moore and Armstrong, 2003; Armstrong and Moore, 2007), who studied influences from the frontal eye field (FEF) upon monkey V4 (see also Winkowski & Knudsen, for a potentially related barn-owl study). But animals may not show the hemispheric asymmetries in function for frontal and parietal cortex that have tentatively been attributed to humans based on clinical evidence (e.g., see Wardak et al., 2004; Wardak et al., 2006). Moreover, to our knowledge, the monkey studies examining frontal influences on visual cortex to date have typically assessed only the right hemisphere (Moore & Armstrong, 2003; Armstrong & Moore, 2007; Moore, personal communication).

Accordingly, here we capitalized on the recent development of concurrent TMS-fMRI in humans (e.g., Shastri et al., 1999; Bohning et al., 1999; Baudewig et al., 2001; Ruff et al., 2006), using this as a novel approach for probing directly whether right versus left human frontal (or intraparietal) cortex can have qualitatively different causal influences on BOLD signal in 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., Pourtois et al., 2001; Grosbras & Paus, 2002; Grosbras & Paus, 2003; Muggleton et al., 2003; O'Shea et al., 2004; Chambers et al., 2004; Muggleton et al., 2006; Silvanto et al., 2006). But 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 vs 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, 2007; see also Paus et al., 1997; Taylor et al., 2007, 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 visual cortex. We found that the impact of left frontal (or parietal) TMS upon BOLD signal in 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 visual cortex, for why TMS (or lesions) to right-hemisphere fronto-parietal 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 extra-striate 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, 2007; see below). This allowed us to compare the impact of left or right frontal/parietal TMS upon human visual cortex for the first time. Inside an MR scanner, TMS was applied at four different intensities over either left frontal cortex (at the putative location of the human frontal eye fields, FEF) or over left parietal cortex (intraparietal sulcus, IPS). We concurrently measured with fMRI any BOLD changes in occipital visual cortex that co-varied 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 human visual cortex could be affected by TMS stimulation of 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 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, 2007), since 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 visual cortex, except via the potential non-specific 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 visual cortex (see also Ruff et al., 2006), which therefore allowed us to directly subtract out any non-specific TMS effects (auditory activations etc.) when considering the results for each 'active' TMS site by itself. For comparison between different 'active' TMS sites, any non-specific 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 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 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 (26 to 35 years of age) as in our previous studies (Ruff et al., 2006, 2007) 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 theBrainsight 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; 2007) 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 et al., 2000) in conjunction with activations during a 5-minute 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 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. Muggleton et al., 2003; O'Shea et al., 2004; Grosbras et al., 2005; Paus, 1996; Ro et al., 1999). For the left-IPS TMS site, we adopted a normalized MNI coordinate ($xyz = -36, -48, 45$) based on the mean coordinates of published activation-peaks in IPS during covert shifts of attention and/or eye-movement planning and execution (taken from Brown et al., 2004; Connolly et al., 2000; Connolly et al., 2002; Corbetta et al., 1998; Curtis et al., 2004; Perry and Zeki, 2000). 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 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, 2007), 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 visual cortex as assessed with fMRI. A 3T 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 1.5T whole-body scanner (Magnetom Sonata, Siemens Medical, Erlangen, Germany) 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 Inc., Boston, Massachusetts, USA) with maximum sensitivity over occipital cortices, as the questions we sought to address here all concerned possible activity changes in visual cortex.

All experimental TMS datasets were acquired with an identical multi-slice gradient echo EPI sequence (27 oblique axial slices, 64×64 matrix, in-plane resolution: $3 \times 3 \text{ mm}^2$, 2.5 mm slice thickness, 1.25 mm spatial gap between adjacent slices, TE=50ms, slice TR 90 ms, 2298 Hz/pixel receiver bandwidth, echo spacing 500 μ s). A 570 ms 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 minutes and 18 seconds.

TMS procedures

TMS was employed inside the MR scanner using a Magstim Super Rapid stimulator and custom-built, figure-of-eight, MR-compatible non-ferrous coils (from the MAGSTIM Company, Dyfed, UK; same as used in Ruff et al., 2006, 2007). 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, Dyfed, UK) 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, Erlangen, Germany). A non-ferromagnetic custom holder with several degrees of freedom in each direction was used to firmly position the TMS coil tangentially over the left-FEF or the 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 ms temporal gap between acquisitions of three subsequent image volumes. The maximum stimulation intensity (85 %) used during scanning only corresponded to 118 % ($\pm$ 14 %) of resting motor threshold for our subjects when applied over 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 twelve control trials without any TMS, during which visual stimuli could be present or absent also. All trials were separated by a constant inter-trial 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 (<http://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 degrees visual angle, grey background, 0.5×0.5 degree 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, 2007), the stimuli were patterns that spared the fovea and the vertical meridian, that randomly changed form and colour every 500 ms, and that randomly moved on each frame (whole-pattern movement, maximum translation in both horizontal and vertical direction of 0.3 degrees per 16 ms 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 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 60Hz during scanning with an ASL 504 remote optics infrared eye tracker (Applied Science Laboratories, Bedford USA). 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 ms) 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 offline, 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 et al., 2001). Any slices containing TMS-capacitor-induced artefacts (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 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 (Montreal Neurological Institute) anatomical standard space and spatially smoothed with a three-dimensional 6mm FWHM Gaussian kernel, in accord with the SPM approach.

Voxel-wise effects of each experimental condition per TMS site were estimated by multiple regression of the voxel time-series onto a composite model with ten 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 seconds cut-off) 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 modelled 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 $p < 0.05$ 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 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, while 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 minute 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 modelled voxel-wise using a general linear model that included the two meridian conditions. The borders of visual areas V1-V4 (Serenio et al., 1995) were then plotted onto cortical flatmaps derived by segmentation and cortical flattening in MrGray (Teo et al., 1997; Wandell et al., 2000). 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 non-specific 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 Schwartz et al., 2005; Ruff et al., 2006, 2007). 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 in particular eccentricity sectors of retinotopic cortex (rather than the less conservative strategy of selecting the peak voxels displaying the maximum effects) allowed us to compare effects between regions and experiments in a spatially unbiased manner.

Visual area V5/MT+ was defined in each participant by means of a separate 5 minute fMRI session with alternating presentations of moving or static starfields. These stimuli spared the fovea by two degrees to each side. A voxel-wise general linear model with two conditions was applied to the unsmoothed data, to determine the cortical region in 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 et al., 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 region-of-interest (ROI) analysis for V5/MT+.

Frontal TMS: Group analyses in stereotactic space

We had previously observed (Ruff et al., 2006) that frontal TMS over right FEF leads to systematic activity increases in the bilateral cuneus (representing the peripheral visual field), but 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 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 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.

Figures 3A show the effects of TMS to left FEF (left histogram) or right FEF (right histogram) on BOLD 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 (dark bars in the histograms of Fig 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). But 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 grey 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 Fig 3A). Moreover, this was not simply a null result, as the impact of left-frontal or 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) $\times 2$ (most central vs most peripheral sector) $\times 2$ (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 ($F_{(1,56)}=35.6$, $p<0.000001$) and a significant interaction of eccentricity sector with stimulation site ($F_{(1,56)}=7.41$, $p<0.01$), 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 $p>0.05$). 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 left or 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 region-of-interest (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 right FEF (see Ruff et al., 2007). 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 occipital visual cortex that differed qualitatively from those due to right frontal TMS (see Ruff et al., 2007). Our new dataset now allowed a direct comparison of the impact of left-versus right-parietal TMS on BOLD signal in occipital visual cortex (analogous to the comparison of left- versus right-frontal TMS data presented above). These new analyses revealed clear hemispheric differences: Whereas right-parietal TMS elicited BOLD signal changes in visual cortex that depended strongly on 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 occipital cortex. Importantly, this new finding was not just a null result, as the patterns found in 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, its right panels); whereas activity decreases due to right parietal TMS were found in lateral occipital cortex (corresponding to V5/MT+ as confirmed further below), only when the moving visual stimuli were *present*, see Figure 4B, its right panels. 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-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 Ruff et al., 2007) in a 2×2 repeated-measures ANOVA (left or right parietal TMS $\times$ visual stimulus present or absent). A significant interaction ($F_{(1,31)}=8.05$, $p<0.01$) 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 ($t_{(1,7)}=2.59$, $p<0.05$), but no effects for left-parietal TMS ($t_{(1,7)}=0.26$, n.s.; see bottom panel of Figure 4B).

Left- versus right-parietal TMS effects for 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 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-parietal TMS had no effect on any retinotopic area (Figure 5A), while 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) $\times 2$ (most central vs most peripheral sector) $\times 2$ (visual stimuli present versus 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, 2007). A significant ($F_{(1,56)}=7.38$, $p<0.01$) interaction between right versus left parietal TMS and absence versus presence of visual stimulation indicated that right parietal TMS affected retinotopic visual cortex in the absence but not 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 $p<0.05$), 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 Fig 5B), and critically also that left parietal TMS did not induce such effects on V1-V4 (all $p>0.88$; 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 visual cortex.

Eye-data Analyses

Eye-position, blinks, and pupil width 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 non-specific effects of TMS upon eye-position, blinks, or pupil dilation could not account for the activity changes observed in visual cortex. As in our previous publications for right-hemisphere TMS (Ruff et al., 2006, 2007), 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 width (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 (Mesulam, 1999; Karnath et al., 2002; Mort et al., 2003; Milner and McIntosh, 2005; Becker & Karnath, 2007) and some purely behavioral TMS studies of neurologically healthy people (e.g., Pourtois et al., 2001; Grosbras & Paus, 2002; Grosbras & Paus, 2003; Muggleton et al., 2003; O'Shea et al., 2004; Chambers et al., 2004; Muggleton et al., 2006; Silvanto et al., 2006) 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 (though see Barcelo et al., 2000). But 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 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 Corbetta & Shulman, 2002; Driver et al., 2004; Kastner & Ungerleider, 2000; Serences & Yantis, 2006, 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 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 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 visual cortex. Our data may thus provide a new possible explanation, in terms of remote physiological effects on visual cortex, for the frequent finding that performance in perceptual tasks is more often affected by TMS to right (rather than left) fronto-parietal cortex in humans (e.g., Pourtois et al., 2001; Grosbras & Paus, 2002; Grosbras & Paus,

2003; Muggleton et al., 2003; O'Shea et al., 2004; Chambers et al., 2004; Muggleton et al., 2006; Silvanto et al., 2006).

While increased intensity of TMS over both 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 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- vs 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 occipital visual cortex in a much more pronounced and distinct fashion than homologous left-hemisphere fronto-parietal regions.

The only significant effect of left-hemisphere TMS on 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 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 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 right frontal cortex for enhancing processing of the peripheral visual field. This might potentially relate to the putative role of frontal cortex in controlling covert spatial attention to the periphery (e.g., Mesulam, 1999; Tehovnik et al., 2000; Juan et al., 2004), 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 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 versus more peripheral) has already been suggested by anatomical tracing studies in the macaque brain (Blatt et al., 1990; Schall et al., 1995; Bullier et al., 1996). But 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 fields’) and for eye-movements (‘motor fields’) (e.g., Schall & Thompson, 1999; Tehovnik et al., 2000; Wardak et al., 2006). Some contra-laterality has also now been suggested for human FEF with fMRI (e.g., Hagler, Jr. & Sereno, 2006; Serences & Yantis, 2007). Nevertheless, this contra-laterality 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 frontal cortex (with TMS) upon activity in remote but potentially interconnected visual cortex.

Our new findings here provide the first evidence that ‘effective connectivity’ of human left and right frontal cortex with 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 vs right frontal cortex might be examined in future studies, such as perhaps with diffusion tensor imaging (DTI) in humans or anatomical tracing techniques in monkeys. For the experiments described here, we had used a surface MR coil centered over occipital cortex, which allowed us to characterize and compare TMS effects on 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 visual cortex described here are unlikely to just reflect fixed effects of monosynaptic anatomical connections of the stimulated sites with visual cortex. For instance, the finding that BOLD changes due to unilateral frontal stimulation arose in visual cortex bilaterally, and even as early as area V1, suggest the involvement of polysynaptic pathways via intervening cortical or subcortical brain regions (for more extensive discussion see Ruff et al., 2006, 2007). 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, i.e., with the functional state of the neuronal circuitry at the time when TMS is applied (see also Bestmann et al., 2007; Friston, 2002; McIntosh, 2000; Massimini et al., 2005; Munchau et al., 2002).

Our results for TMS to the parietal sites revealed even more striking evidence that right-hemisphere TMS can result in influences upon 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 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 and areas in 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., Culham, Cavanagh, and Kanwisher 2001; Kastner and others 1999; Macaluso and Driver 2005; Shulman et al., 2003; Wardak and others 2006). Context-dependence of effective connectivity between 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 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 retinotopic-IPS connections 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 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, since deficits such as neglect or extinction are most often reported after lesions of right-hemisphere brain areas in and around parietal cortex and the IPS, whereas lesions of corresponding parietal regions in the left hemisphere rarely have such effects (Mesulam, 1999; Karnath et al., 2002; Mort et al., 2003; Milner & McIntosh, 2005; Becker & Karnath, 2007). Our findings provide a possible new interpretation of such clinical lesion data, namely that the marked effects of lesions to right-hemisphere regions of human parietal cortex may relate to the specific capacity of these regions for functional influences upon visual cortex. This interpretation could also fit with some of the clinical sequelae of right-parietal damage (e.g., extinction) depending on current visual context (see e.g., Mesulam, 1999; Vuilleumier & Rafal, 2000; Marzi et al., 2001; Driver, Vuilleumier & Husain, 2004), as established also for the right-parietal TMS effects upon 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 (Pourtois et al., 2001; Grosbras & Paus, 2002; Grosbras & Paus, 2003; Muggleton et al., 2003; O'Shea et al., 2004; Chambers et al., 2004; Muggleton et al., 2006). 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 remote visual cortex. Our new results here provide direct evidence that 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 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 et al. 2008; Sack et al., 2007).

In contrast to lesion and TMS investigations in humans, studies in non-human 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., Moore & Fallah, 2004; Wardak et al., 2004; Wardak et al., 2006). Hemispheric differences in effects of TMS on perceptual behavior, and remote impact upon visual cortex as described here, may reflect some aspects of hemispheric specialization that are potentially unique to the human brain (Hellige, 1990; Davidson & Hugdahl, 1995; Sun & Walsh, 2006). 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 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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Figure 1. TMS sites in individual participants and experimental design

Panel (A) shows 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, 2007; blue for right FEF, green for right IPS, and white for the vertex control site). Panels (B) and (C) show a schematic timecourse (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 grey screen. For each block, three TMS trains were delivered in the 570 ms 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 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.

Figure 2. Group analyses of frontal-TMS data: Occipital regions displaying activity changes correlating with intensity of TMS over left or right FEF

Panels in (A) show all occipital regions that displayed reliable BOLD-signal decreases with increased intensity of frontal TMS over 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 $p < 0.05$, corrected across the brain volume. In the bottom panel, a rendering of these SPM(T)s onto a standard 3D 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). Panels in (B) show the outcome when testing instead for BOLD-signal increases with increased intensity of frontal TMS over the left or right FEF. Whereas medial occipital cortex (representing the peripheral visual field) showed such an influence during right frontal TMS over FEF (shown in the cutaway 3D 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

Panels in (A) show the pattern of effects of TMS to 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, 2007) was averaged across flatmaps and voxels within each eccentricity sector of areas V1-V4. These average correlations ($\pm$ s.e.m) 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 dorsal and ventral cuneus. In all these retinotopic visual areas, increased TMS-intensity over 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 (* $p < 0.05$, + $p < 0.1$ in simple t-tests). Panel (B) shows 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 (n.s. = not significant); whereas the TMS-induced activity increases in the peripheral sector were consistently stronger during right than left frontal TMS (* $p < 0.05$, + $p < 0.1$ in paired t-tests).

Figure 4. Group analyses of parietal-TMS data: Right- but not left-parietal TMS elicits BOLD changes in visual cortex that depend on current visual context

Panels (A-B) show 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 $p < 0.05$, 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 is shown on the right. The line plots displayed at the bottom of Panel (A) show the mean signal intensity ($\pm$ s.e.m.) during the different experimental conditions, as extracted from a spherical region-of-interest (6mm radius) centered in the peak medial cuneus voxel of the SPM(*T*) for the right-parietal TMS data shown above. Note that significant BOLD decreases ($p < 0.05$ 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 (n.s. = not significant). In both experiments, the medial 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. The line plots displayed at the bottom of panel (B) show the mean BOLD signal intensity ($\pm$ s.e.m.) during left or right parietal TMS in area V5/MT+, as determined for each subject with a fMRI motion localizer (see Methods, signal is pooled over hemispheres since all effects were symmetric and bilateral). Increased intensity of right-parietal TMS led to significant ($p < 0.05$ in paired-*t*-tests, marked by a star) activity decreases in V5/MT+ only when the moving visual stimuli were present (green lines), 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).

Figure 5. Retinotopic analyses of parietal-TMS influences on visual areas V1-V3: 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 ($\pm$ s.e.m) 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, panel (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 (* $p < 0.05$, + $p < 0.1$ in paired t-tests). Panel (C) shows 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 visual cortex.