Behavioral/Systems/Cognitive

Frontoparietal Cortex Controls Spatial Attention through Modulation of Anticipatory Alpha Rhythms

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A dorsal frontoparietal network, including regions in intraparietal sulcus (IPS) and frontal eye field (FEF), has been hypothesized to control the allocation of spatial attention to environmental stimuli. One putative mechanism of control is the desynchronization of electroencephalography (EEG) alpha rhythms (~8–12 Hz) in visual cortex in anticipation of a visual target. We show that brief interference by repetitive transcranial magnetic stimulation (rTMS) with preparatory activity in right IPS or right FEF while subjects attend to a spatial location impairs identification of target visual stimuli ~2 s later. This behavioral effect is associated with the disruption of anticipatory (prestimulus) alpha desynchronization and its spatially selective topography in parieto-occipital cortex. Finally, the disruption of anticipatory alpha rhythms in occipital cortex after right IPS- or right FEF-rTMS correlates with deficits of visual identification. These results support the causal role of the dorsal frontoparietal network in the control of visuospatial attention, and suggest that this is partly exerted through the synchronization of occipital visual neurons.

Introduction

Observers develop spatial expectations about visual scenes that guide and enhance perception (Eriksen and Hoffman, 1972; Posner, 1980). Neuroimaging studies have suggested that spatial attention biases perception through an interaction between "control" regions in dorsal frontoparietal cortex which generate and maintain expectations and occipital visual regions involved in sensory analysis (Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002; Serences and Yantis, 2006). Recent studies have directly shown this interaction using electrical micro-stimulation (Moore and Armstrong, 2003; Moore and Fallah, 2004), TMS (Ruff et al., 2006, 2008), or analyses of directional mutual information on blood oxygenation level-dependent (BOLD) signal time series (Bressler et al., 2008).

The neuronal mechanism through which higher-order control areas take control of visual neurons is unknown. Spatial attention may control visual cortex by synchronization of inputs or modulation of the temporal coherence of ongoing oscillatory activity (Engel et al., 2001; Fries, 2005). A putative marker of the physiological interaction between frontoparietal regions and occipital visual areas is the modulation of the posterior alpha rhythms as recorded with electroencephalography (EEG). These rhythms show high power over parieto-occipital area in the absence of visual stimulation (Steriade and Llinás, 1988) which is then reduced in anticipation of visual targets (Klimesch et al., 1998). When subjects expects a target at a specific location the topography of alpha rhythms becomes spatially selective (Worden et al., 2000; Yamagishi et al., 2003; Sauseng et al., 2005; Thut et al., 2006), and predicts trial-by-trial the locus of attention and visual performance (Thut et al., 2006).

Here, we test the hypothesis that frontoparietal regions control spatial attention in visual cortex through the anticipatory desynchronization of ongoing alpha rhythms. We predict that disruption by rTMS of neural activity in frontoparietal regions during the allocation of spatial attention will interfere both with the subsequent perception of visual stimuli and the desynchronization of alpha rhythms in occipital cortex, monitored by simultaneous recordings of EEG activity. The effect of interference in dorsal frontoparietal regions, IPS and FEF, core regions of the "dorsal attention network" (Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002), is contrasted with the effects on a precentral (PrCe) region part of a "ventral attention network"(Corbetta and Shulman, 2002; Corbetta et al., 2008). This is a right hemisphere dominant network involved in reorienting attention to relevant sensory stimuli, but not in directing attention based on endogenous expectations. Previous fMRI studies have reported robust attention-related activity in right FEF, following the presentation of a spatial cue and before the presentation of a target stimulus (delay activity), but not in right PrCe (Corbetta et al., 2002, 2005; Kincade et al., 2005). Right PrCe is therefore an excellent control region for FEF given its anatomical proximity but different physiological profile. Given the ventral network is right hemisphere dominant, as well as for safety reasons related to the total dose of rTMS, we limited the stimulation to the right hemisphere.

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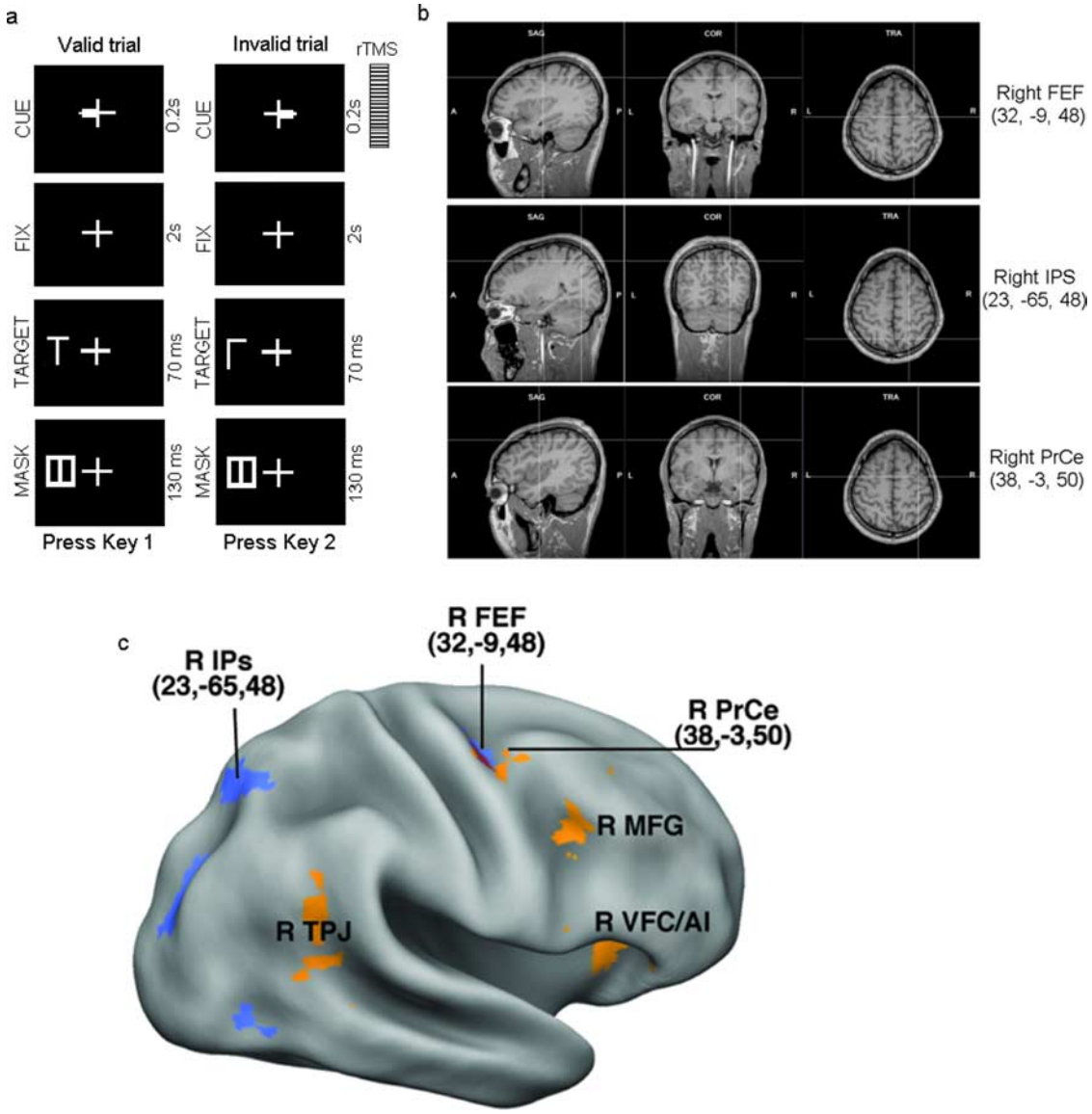

Figure 1. Task and rTMS localization. ***a***, Sequence of events during a trial. ***b***, Magnetic resonance imaging (MRI)-constructed stereotaxic template showing the sagittal (***a***), coronal (***b***), and axial (***c***) projections of the three rTMS sites on the right hemisphere. ***c***, Inflated view of right hemisphere atlas brain with regions of dorsal and ventral attention network as in meta-analysis of He et al. (2007). Regions with coordinates are stimulated with rTMS in this experiment.

Materials and Methods

Subjects. Sixteen right-handed (Edinburgh Inventory) healthy adult volunteers (age range: 20–30 years old; 3 females) with no previous psychiatric or neurological history participated in the main experiment. Their vision was normal or corrected to normal. All experiments were conducted with the understanding and written consent of each participant according to the Code of Ethics of the World Medical Association, and the standards established by the University of Chieti Institutional Review Board and Ethics Committee. A second behavior-only control experiment involved 9 right-handed healthy volunteers (age range: 24–33 years old; 5 females), and checked for visual field differences in stimulus identification (see below). Finally, we enrolled an additional 8 right-handed healthy adult volunteers (age range: 22–31 years old; 4 females) in a separate rTMS experiment designed to control for the effects of cue encoding/attention shifts (see below).

Experimental task. All studies were conducted at the Institute of Technology and Advanced Bioimaging (ITAB) by the first author (P.C.). The subjects were seated in a comfortable reclining armchair and kept their arms resting on the keyboard of a computer. The computer monitor was placed in front of them at a distance of ~80 centimeters. The experimental paradigm is shown in Figure 1*a*. Subjects maintained fixation on a small white cross (subtending 0.7° of visual angle), displayed on a black background at the center of the screen. Every 5.9 ± 1 s (sec) a cue stimulus (a white small filled rectangle subtending ~0.2° visual angle and overlapping the left or right horizontal segment of the fixation cross) was presented for 200 ms duration, cueing randomly (50%) either a left or right visual field location. After 2 s (stimulus onset asynchrony, SOA), a target stimulus was briefly presented for 70 ms at one of two target locations positioned in the left or right visual field along the horizontal meridian at 0.7° degrees of visual angle from the fixation point. The target stimulus was either the letter L (50%) or the letter T (50%) shown either in the canonical upright orientation (50% of trials) or rotated 180 degrees along the vertical axis (the other 50%). Both letters had a diameter of 0.7° visual angle. The target stimulus appeared on 80% of the trials at the location indicated by the cue (valid trials), and on 20% of the trials at the uncued location (invalid trials) (Posner, 1980). Immediately after the target stimulus, a mask stimulus (130 ms duration) formed by all the possible line segments forming the letter stimuli L or T was presented to interrupt the visual processing of the target shape. The subject's task was to maintain fixation throughout the trial, pay attention covertly to the

location indicated by the cue, and discriminate the shape of the target by pressing a left keyboard button (key A) when they saw the letter T (upright or rotated), and a right keyboard button (key L) when they saw the letter L (upright or rotated). The assignment of "target" (T or L) to the specific key for response (A or L) was randomized across subjects. Moreover, subjects were asked to maintain the hands on the keyboard and the sight fixed on the screen so that they could not really see the keyboard. The spatial cue indicated the position of the stimulus, but did not provide any information about the response. This is important to insure that preparatory processes are indeed visuospatial and not motor in origin (Broadbent, 1971). Reaction times and the accuracy of the response were recorded for behavioral analyses.

Procedures for rTMS and identification of target scalp regions. To interfere with neural activity during the allocation of spatial attention, we used repetitive transcranial magnetic stimulation (rTMS). The stimulation was delivered through a focal, figure eight coil (outer diameter of each wing 7 cm), connected with a standard Mag-Stim Rapid 2 stimulator (maximum output 2.2 tesla). Individual resting excitability threshold for right motor cortex stimulation was preliminarily determined by following standardized procedure (Rossini et al., 1994; Rossi et al., 2001). The rTMS train was delivered at the onset of the cue stimulus based on the following parameters: 150 ms duration, 20 Hz frequency, and intensity set at 100% of the individual motor threshold. These parameters are consistent with published safety guidelines for TMS stimulation (Wassermann, 1998; Anderson et al., 2006; Machii et al., 2006). While previous studies have successfully used rTMS for studying the role of prefrontal and parietal cortices in target detection and reorienting of attention to sensory stimuli (Pascual-Leone et al., 1994; Hilgetag et al., 2001; Rushworth et al., 2001; Grosbras and Paus, 2002, 2003; Chambers et al., 2004; Thut et al., 2005; Taylor et al., 2007), this experiment concentrates on the anticipatory delay activity between cue and target stimuli.

The experimental design included four conditions of rTMS, pseudo-randomized across subjects. In the "Sham" condition, a pseudo-rTMS was delivered at scalp vertex; it was ineffective due to the reversed position of the coil with respect to the scalp surface (i.e., the magnetic flux was dispersed to air). In the FEF, IPS, and PrCe conditions, rTMS interfered with activity at the predetermined scalp sites since we placed the anterior end of the junction of the two coil wings. A mechanical arm maintained the handle of the coil angled at ~45° away from the midline.

The location of right FEF, IPS, and PrCe locations was automatically identified on the subject's scalp using the SofTaxic navigator system (E.M.S. Italy, www.emsmedical.net), which uses a set of digitized skull landmarks (nasion, inion, and two preauricular points), and ~30 scalp points entered with a Fastrak Polhemus digitizer system (Polhemus), and an averaged stereotaxic MRI atlas brain in Talairach space (Talairach and Tournoux, 1988). The average Talairach coordinates in the SofTaxic navigator system were transformed through a linear transformation to each individual subject's scalp. This strategy has been successful in previous rTMS studies of posterior parietal cortex and visuospatial attention (Babiloni et al., 2006).

The coordinates of the different cortical regions were based on a recent meta-analysis of task-evoked studies of spatial attention (He et al., 2007) and were as follows: right FEF: 32, −9, 48 (*x*, *y*, *z*); right IPS: 23, −65, 48; right PrCe: 38, −3, 50 (Fig. 1*b*). The chosen coordinates correspond respectively to the epicenters of the two core regions of the dorsal attention frontoparietal network (IPS, FEF), and one control region in the ventral attention network (PrCe) just lateral and anterior to FEF (vector distance = 8.7 mm) (Fig. 1*c*). The center of mass of these regions, although close, are reliably different across subjects as they were derived from a meta-analysis of several converging fMRI studies [$N = 4$ studies including >80 subjects, as described by He et al. (2007)].

Right PrCe is an ideal control region for several reasons. It is part of the ventral attention network that responds to the presentation of targets especially when relevant and unattended. It has been proposed that the ventral attention network contributes a signal for reorienting attention to important stimuli in the environment or "stimulus-driven reorienting" (Corbetta and Shulman, 2002; Corbetta et al., 2008). Therefore, similarly to FEF, right PrCe is sensitive to visual stimuli and attention shifts; but, unlike FEF, it does not respond when these shifts are driven by endogenous expectancies. Its location <1 cm away from FEF (see Fig. 1*b*,*c*) makes it ideal to study the effect of rTMS on occipital alpha rhythms given both regions are approximately at the same distance from the parieto-occipital cortex where the alpha rhythms are more prominent.

Electroencephalography recordings. To assess the physiological impact of rTMS on anticipatory neural activity, we recorded simultaneously EEG activity from the scalp. Specifically, we measured the effect of magnetic stimulation at different cortical loci on the desynchronization of alpha rhythms in parieto-occipital cortex, a reliable physiological index of anticipatory spatial attention modulation (Worden et al., 2000; Yamagishi et al., 2003; Sauseng et al., 2005; Thut et al., 2006).

EEG data were recorded (BrianAmp; bandpass, 0.05–100 Hz, sampling rate, 256 Hz) from 27 EEG electrodes placed according to an augmented 10–20 system, and mounted on an elastic cap resistant to magnetic pulses. Electrode impedance was <5 KΩ. The artifact of magnetic stimulation on the EEG activity lasted ~10 ms (supplemental Fig. 4*a*, available at www.jneurosci.org as supplemental material). Two electrooculographic channels were used to monitor eye movement and blinking. The acquisition time for all data was set from −2 to +2 s after cue stimulus. Approximately 120 EEG trials were collected for each rTMS stimulation site and for each subject. The EEG single trials contaminated by eye movement, blinking, or involuntary motor acts (e.g., mouth, head, trunk, or arm movements) were rejected off-line. To remove the effects of the electric reference, EEG single trials were rereferenced by the common average reference. The common average procedure includes the averaging of amplitude values at all electrodes and the subtraction of the mean value from the amplitude values at each single electrode. The mean number of trials per condition that were artifact-free data was 92 (±11).

Computation of the event-related desynchronization/synchronization. For the EEG spectral analysis, the frequency bands of interest were low alpha and high alpha. These frequencies were determined in according to a standard procedure based on the peak of individual alpha frequency (IAF) (Klimesch et al., 1998). With respect to the IAF, these frequency bands were defined as follows: (1) low alpha, IAF − 2 Hz to IAF, and (2) high alpha, IAF to IAF + 2 Hz. This power spectrum analysis was based on an FFT approach using the Welch technique and Hanning windowing function. The length of the EEG periods used as an input for FFT was of 1 s. The event-related desynchronization/synchronization (ERD/ERS) of alpha EEG oscillations was obtained using:

$$\mathrm{ERD\%} = (E - R)/R \times 100,$$

where E indicates the power density at the "event" (lasting 1 s) and R the power density at the "rest" (lasting 1 s). The ERD/ERS was computed for the IAF-based low and high alpha (supplemental Fig. 4*b*, available at www.jneurosci.org as supplemental material). The "rest" of ERD/ERS computation was defined as a period from −1.5 to −0.5 s before the cue stimulus. The "event" of ERD/ERS computation was defined as a period from 0.5 to 1.5 s after the cue stimulus. Topographic maps of the alpha ERD/ERS were calculated in the period following the cue stimulus and rTMS stimulation (from 0.5 to 1.5 s after cue onset). The maps were represented on a 3D template cortical model by a spline interpolating function. This model is based on the magnetic resonance data of 152 subjects digitized at Brain Imaging Center of the Montreal Neurological Institute (SPM96).

Statistical analysis. Statistical comparisons were performed by ANOVAs for repeated measures. We used a Mauchley's test to evaluate the sphericity assumption of the ANOVA, a Green-house-Geisser procedure for the correction of the degrees of freedom based, and Duncan tests for *post hoc* comparisons (alpha, $p < 0.05$). For the behavioral analyses on the effects of rTMS we used reaction times (RTs) or percentage of correct responses (Hits) with Condition (Sham, right PrCe, right FEF, right IPS), Side (target stimulus on the right or left side of the screen), and cue Validity (valid or invalid trials) as within-subject factors.

To verify the normal hemispheric lateralization of anticipatory alpha rhythms in parieto-occipital electrodes, we ran an ANOVA for each Condition (Sham, right PrCe, right FEF, right IPS), using the alpha ERD/ERS, separately for low and high alpha sub-bands, respectively, as dependent

variable and Hemisphere (contra or ipsi to cue stimulus), and Electrode of interest (parietal or occipital) as within-subject factors,

To test the influence of rTMS on anticipatory EEG alpha rhythms, we used alpha ERD/ERS, separately for low and high alpha sub-bands, respectively, as dependent variable and Condition (Sham, right PrCe, right FEF, right IPS), Hemisphere (right or left hemisphere), and Electrode of interest (parietal or occipital) as within-subject factors.

To test for significant relationships between electrophysiological measures and visual performance, we computed a correlation analysis (Pearson test, $p < 0.05$) between alpha ERD/ERS (at electrodes P3, P4, O1, O2) during the cue period, and RTs to target stimuli. For this analysis, alpha ERD/ERS values obtained for the three conditions of active rTMS stimulation (right FEF, IPS, PrCe) were normalized with respect to those obtained in the Sham condition according to the following formula: rTMS site − Sham/rTMS site + Sham. This normalization insured that we correlated with behavior the specific changes induced by rTMS over different cortical sites above or below the physiological modulation observed in Sham. The two alpha sub-bands were considered separately (i.e., low- and high-frequency). We used the same formula for the normalization of RTs.

A significant correlation across subjects suggest that the modulation of alpha ERD/ERS induced by rTMS covaries with behavioral performance differently in different individuals. A more stringent relationship is to show a correlation within each subject on a trial-by-trial basis. Trial-by-trial analyses are limited in EEG by low signal-to-noise, but we circumvented this problem through the following procedure. Trials for canonical and rotated targets, which yield on average faster and slower RT, respectively, were separately ranked in faster or slower RTs than the median value. ERD/ESR % change values for each group of trials (faster, slower) and for each condition (canonical, rotated) were averaged to generate four mean alpha ERD/ERS values, one for each category, i.e., canonical-fast, canonical-slow, rotated-fast, rotated-slow. For each stimulation site (FEF, IPS, PrCe, Sham), we ran a within-subject ANOVA on the ERD/ERS % change during the period preceding the target stimuli with Stimulus (canonical, rotated), RT (fast, slow) and electrodes (P3, O1, P4, O2) as within-factors.

Several control analyses were also performed. One ANOVA compared the size of the early sensory evoked components (P1/N1) across conditions for valid trials. Unfortunately, we did not have enough artifact-free trials to perform a proper random-effect analysis of the target-related P1/N1 component comparing valid and invalid trials. Invalid trials were only a small proportion (20%) of the total number of trials and invalid targets were detected with lower accuracy. Another ANOVA compared power changes in the period preceding the cue used to calculate a baseline to verify that rTMS at different cortical sites did not affect the baseline alpha power in both low and high-frequency sub-bands. The ANOVA factors were Condition (Sham, PrCe, FEF and IPS), hemisphere (left, right), and electrodes (P3, O1, P4, O2).

Control experiment. In a separate rTMS experiment the stimulation was delivered as Sham or on right IPS at two different times: simultaneously to the onset of the cue stimulus (R-IPS $t_{(0)}$), or 350 ms after the cue (R-IPS $t_{(350)}$). The parameters of rTMS and the task were identical to the main experiment. ANOVAs were run with reaction times (RTs) or percentage of correct responses (Hits) as dependent variable, and Condition (Sham, R-IPS $t_{(0)}$, and R-IPS $t_{(350)}$), and cue Validity (valid or invalid trials) as within-subject factors.

Results

Behavior

We assessed the effects of rTMS delivered at the onset of a spatial cue directing attention to a peripheral location on the accuracy and reaction time (RTs) of target identification ~1.5 s later (Fig. 2). The effects of rTMS were different at different cortical sites

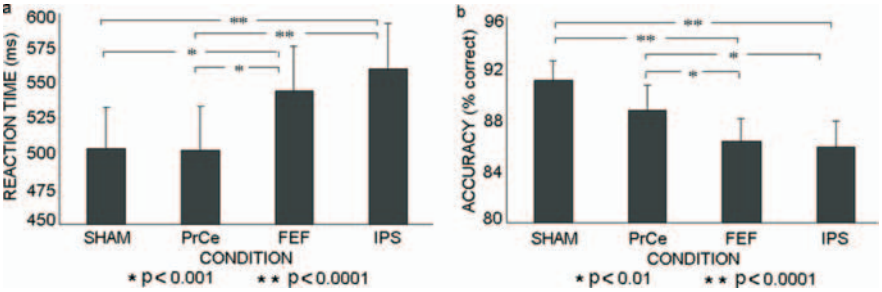

Figure 2. Behavioral effects of rTMS at different cortical sites. ***a***, Group means (±SE) of the reaction time (in milliseconds). Duncan *post hoc* tests: * $p < 0.001$, ** $p < 0.0001$. ***b***, Group means (±SE) of the accuracy (%).

both in terms of RTs ($F_{(3,45)} = 11.19$; $p < 0.0001$) and accuracy of target identification ($F_{(3,45)} = 10.88$; $p < 0.0001$). Magnetic stimulation on right FEF (544 ± 31 ms) and right IPS (560 ± 32 ms) significantly slowed down target responses compared with Sham (524 ± 29 ms; $p < 0.001$ vs FEF; $p < 0.0001$ vs IPS) or right PrCe stimulation (502 ± 31 ms; $p < 0.001$ vs FEF; $p < 0.0001$ vs IPS). There was no significant difference between right PrCe and Sham stimulation (Fig. 2*a*). Correct responses also occurred less frequently after rTMS on right FEF (86.3% ±1.7) and right IPS (85.9 ± 1.9%) than after Sham (91.1 ± 1.1%; $p < 0.0001$ vs FEF; $p < 0.0001$ vs IPS) or right PrCe stimulation (88.7 ± 1.9%; $p < 0.01$ vs FEF; $p < 0.01$ vs IPS) (Fig. 2*b*).

rTMS did not disrupt the observers' ability to direct spatial attention to the target location. In fact there was an overall significant main effect of target validity (RTs: valid, 503 ± 30 ms; invalid, 552 ± 32 ms; $F_{(1,15)} = 14.84$ $p < 0.002$; accuracy: valid, 90.4% correct ± 1.5; invalid, 85.6% correct ± 2 $F_{(1,15)} = 16.74$ $p < 0.001$). However, rTMS of right FEF and right IPS more strongly impaired target detection at unattended (invalidly cued) locations (Accuracy: Validity × rTMS Condition, $F_{(3,45)} = 2.74$ $p = 0.054$) (supplemental Fig. 1, available at www.jneurosci.org as supplemental material).

The effect of rTMS at different cortical sites was not differential for left (contralateral) or right (ipsilateral) visual field targets. However, targets presented in the right visual field were identified overall more accurately and more rapidly than targets presented in the left visual field (left VF: 507 ms ± 30.5; right VF: 499 ± 30 ms $F_{(1,15)} = 18.64$ $p < 0.0005$; accuracy: left VF: 90% correct ± 1.6; right VF: 91% correct ± 2 $F_{(1,15)} = 4.97$ $p < 0.05$) (supplemental Fig. 2, available at www.jneurosci.org as supplemental material; for a complete picture of behavioral results divided by site of stimulation, target visual field, and cue validity, see supplemental Fig. 3, available at www.jneurosci.org as supplemental material).

The visual field lateralization may relate to the well known superiority of the right visual field (left hemisphere) for alphabetical material (Rizzolatti et al., 1971). To insure that this effect did not depend on magnetic stimulation, we ran a novel group of healthy volunteers ($N = 9$) without rTMS. Once again right visual field targets were detected faster and more accurately than left visual field targets (RTs: left VF: 663 ms ± 37.4; right VF: 612 ± 40 ms $F_{(1,8)} = 30.52$ $p < 0.001$; accuracy: left VF: 86% correct ± 2.75; right VF: 93% correct ± 1.8 $F_{(1,8)} = 5.49$ $p < 0.05$).

Finally, to verify that the behavioral deficits induced by rTMS in prefrontal and posterior parietal cortex did not reflect a cumulative effect building up over many trials, but actually reflected interference with preparatory processes on a trial-by-trial basis, we checked whether the size of the deficit differed in the first, second, third, and fourth quartile of each block of trials, and

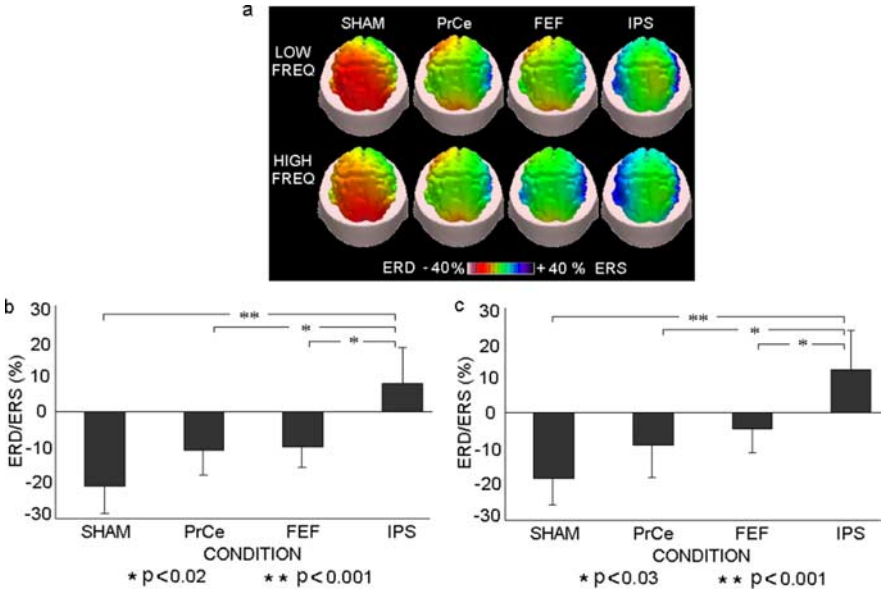

Figure 3. Topography of alpha power as function of rTMS conditions. ***a***, Topographic maps of anticipatory low and high alpha ERD/ERS during the cue period (+500–2000 ms after the onset of the cue). ***b***, Group means (±SE) of the low alpha ERD/ERS. Duncan *post hoc* tests: $*p < 0.05$, $**p < 0.001$. ***c***, Group means (±SE) of the high alpha ERD/ERS.

found no difference. Although this null result does not rule out that a cumulative effect occurred, it is more consistent with the notion that rTMS mainly interfered on the trial in which it was applied.

Overall these findings indicate that interference with preparatory processes in FEF and IPS during anticipatory visuospatial attention significantly altered visual perception of targets presented two seconds later in both visual fields.

EEG

The EEG signals chosen for the analysis of alpha rhythms (+0.5 s to +1.5 s after cue onset) were free of rTMS artifacts. supplemental Figure 4*a* (available at www.jneurosci.org as supplemental material) shows EEG data at parietal and occipital electrodes of interest (P3, P4, O1, O2) from a single subject in the four conditions (Sham, right FEF, right IPS, right PrCe). The rTMS artifact practically lasted the stimulation period (150 ms) plus ~10 ms. Supplemental Figure 4*b* (available at www.jneurosci.org as supplemental material) shows EEG power spectra (3–40 Hz, 1 Hz resolution) for the "baseline" (−1.5 s to −0.5 s before the cue stimulus onset) and the "cue event" period (+0.5 s to 1.5 s). The alpha frequency peak is clearly recognizable at all electrodes of interest, and the profile of the EEG spectra looks regular.

The main question of the study was whether anticipatory alpha rhythms in occipital visual cortex were affected by interference with neural activity in control regions, IPS and FEF, during a delay in which subjects covertly attended to a target location. Figure 3*a* illustrates the topography of parieto-occipital alpha ERD/ERS in the four conditions (Sham, right FEF, right IPS, right PrCe), during the anticipation of the target. During Sham, we observed a robust bilateral ERD (desynchronization) at both low- and high-frequency alpha sub-bands in parietal-occipital cortex. A weak anticipatory alpha ERD was also observed after rTMS on right FEF and right PrCe. In contrast, right IPS-rTMS abolished the normal desynchronization which was substituted by a paradoxical synchronization, or bilateral increase of alpha power (ERS). This qualitative impression was confirmed by statistical analysis. For the low-frequency alpha ERD/ERS (Fig. 3*b*), an ANOVA showed a significant main effect of site of stimulation ($F_{(3,45)} = 5.96$; $p < 0.002$). This was accounted for by a greater anticipatory alpha power (ERS) for right IPS than Sham ($p < 0.001$), right PrCe ($p < 0.02$), or right FEF stimulation ($p < 0.02$) regardless of electrodes of interest (occipital, parietal) or hemisphere (left, right). The same effect was observed for the high-frequency alpha ERD/ERS ($F_{(3,45)} = 6.10$; $p < 0.002$) with greater anticipatory alpha ERS for right IPS than Sham ($p < 0.001$), right PrCe ($p < 0.03$), or right FEF ($p < 0.03$) stimulation (Fig. 3*c*). In summary, interference with right IPS preparatory activity during spatial attention abolished the normal anticipatory desynchronization of alpha rhythms in parieto-occipital cortex.

Next, we examined whether IPS- or FEF-rTMS changed the spatially selective topography of alpha desynchronization in parieto-occipital cortex (Worden et al., 2000; Sauseng et al., 2005; Yamagishi et al., 2005; Thut et al., 2006). As predicted by previous studies, anticipatory alpha ERD in the high-frequency sub-band was stronger over the hemisphere contralateral to the side of attention during Sham ($F_{(1,15)} = 13.60$; $p < 0.003$). Interestingly, a significant contralateral topography was still present after right PrCe stimulation ($F_{(1,15)} = 6.37$; $p < 0.03$), but was completely disrupted by stimulation of both right FEF and right IPS (Fig. 4).

If the physiological disruption of anticipatory alpha rhythms in occipital cortex after disruption of attention-delay activity in right FEF and right IPS is functionally significant, then we would expect a positive relationship between changes in alpha ERD/ERS and visual performance. A Pearson correlation analysis was run between parieto-occipital alpha ERD/ERS (at electrodes P3, P4, O1, O2) during the cue period, and RTs to target stimuli separately for each stimulation site. Only in the case of right IPS stimulation we found a positive correlation between low-frequency alpha ERD/ERS at the P3 electrode (left parietal region contralateral to the rTMS stimulation) and RTs ($r = 0.61$ $p < 0.01$) (Fig. 5*a*). A second positive correlation was found between high-frequency alpha ERD/ERS at the O1 electrode (left occipital region contralateral to the rTMS stimulation) and RTs ($r = 0.58$ $p < 0.02$) (Fig. 5*b*). These findings suggest that subjects with higher paradoxical synchronization of occipito-parietal cortex after right IPS stimulation tend to identify the target letters more slowly. This relationship is predictive in the sense that the ERD/ERS changes produced by rTMS precede in time the identification of the target.

To more stringently correlate disruption of anticipatory alpha rhythms with target discrimination, we carried out, separately for each stimulation site (Sham, IPS, FEF, PrCe), a within-subject ANOVA with Stimulus (canonical, rotated), RT (fast, slow), and Electrode (P3, O1, P4, O2) as factors (see Materials and Methods). Only in right FEF we found a significant interaction of Stimulus × RT × Electrode ($F_{(3,45)} = 2.99$; $p < 0.04$) in the high-frequency alpha ERD/ERS (Fig. 6*a*,*b*). For targets that were more difficult to discriminate (rotated L or T), there was a stronger paradoxical synchronization after right FEF-rTMS on right parietal (P4) and right occipital (O2) electrodes when subjects

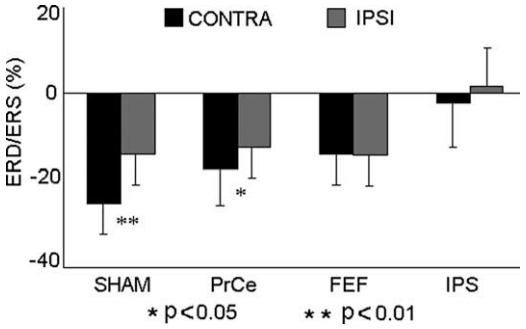

Figure 4. Contralateral spatial selectivity of alpha power by rTMS condition. Group means (±SE) of the high alpha ERD/ERS for the four Conditions (Sham, Right PrCe, Right FEF, Right IPS) divided by Hemisphere (contra or ipsi to cue stimulus).

were slower to respond; in contrast, a normal desynchronization occurred when subjects responded more quickly to the same stimuli (Fig. 6*b*). In contrast, for canonical letters associated with faster responses and likely requiring less attentional scrutiny, a normal desynchronization was observed in parieto-occipital cortex (Fig. 6*a*). A predictive relationship between disruption of anticipatory alpha rhythms and behavioral performance after right FEF-rTMS was also confirmed across subjects, with a positive correlation between parieto-occipital high-frequency alpha ERD/ERS (at electrodes P4, O2) and slow RTs for rotated targets. As shown in Figure 5*c*, across-subjects higher alpha power at the P4 electrode (right parietal) after right FEF stimulation was positively correlated with slower ($r = 0.49$, $p = 0.05$) (Fig. 6*c*, red dots), but not faster RTs (Fig. 6*c*, black dots).

Overall these results suggest a strong link between disruption of right FEF preparatory activity, interference with parieto-occipital anticipatory alpha rhythms, and target discrimination. While disruption of IPS preparatory activity may have a more general effect on alpha desynchronization and target detection, preparatory activity in FEF may play an especially important role when visual selection/discrimination is more demanding.

A potential alternative interpretation of our results is that rTMS affects visual perception not by disrupting preparatory processes during the delay, but target evoked activity. We performed a control analysis on the earlier components of parieto-occipital potentials evoked by the target stimulus (P1, N1). The amplitude and latency of the P1-N1 complex were not affected by rTMS during the cue period ($p > 0.6$) (supplemental Fig. 5, available at www.jneurosci.org as supplemental material) at any of the sites. Hence visual discrimination impairment was not related to impaired target processing, but disrupted selection.

A second control analysis ruled out that changes in alpha power during the attention delay were not due to changes of the baseline before cue onset (see Materials and Methods). This result was confirmed for both low and high-frequency alpha subbands ($p > 0.5$ in both cases).

Control experiment

Given the rTMS train was presented coincident with the onset of the cue, an alternative explanation of the behavioral deficits induced by right IPS (and FEF) stimulation was that rTMS disrupted the sensory processing of the cue, the interpretation of its directional information, or the initial shift of attention. Although in the main experiment all subjects reported seeing clearly the cue stimulus, and all modulations on alpha rhythms (and related behavioral correlation) were measured from 0.5 to 1.5 s after the onset of the cue, these alternative interpretations, proposed by one of the reviewers, could not be ruled out with the present data set.

In a control experiment on 8 new right-handed healthy volunteers rTMS was delivered as either Sham or on right IPS at two different times: simultaneously to the onset of the cue stimulus (R-IPS $t_{(0)}$), or 350 ms after the cue (R-IPS $t_{(350)}$). If the behavioral deficits reported in the main experiment reflect ongoing preparatory processes during the delay, then similar effects should be measured at both intervals. Alternatively, if the behavioral deficits underlie transient processes occurring at the onset of the cue (e.g., cue encoding or shift of attention) then weaker effects should be obtained when the rTMS train is delivered later in the delay.

Regardless of timing, we replicated the deficits produced on response speed (RTs: $F_{(2,14)} = 4.92$; $p < 0.025$)) and identification accuracy (%correct: $F_{(2,14)} = 7.03$; $p < 0.01$) by right IPS-rTMS (supplemental Fig. 6, available at www.jneurosci.org as supplemental material). When the stimulation was delivered simultaneously to the onset of the cue (R-IPS $t_{(0)}$: 596 ± 44 ms) or later in the delay (R-IPS $t_{(350)}$: 603 ± 40 ms), target RTs were significantly slower compared with Sham (560 ± 38 ms; $p < 0.03$ vs R-IPS $t_{(0)}$; $p < 0.03$ vs R-IPS $t_{(350)}$). There was no significant difference between R-IPS $t_{(0)}$ and R-IPS $t_{(350)}$ (Fig. 7*a*). Correct responses were also less frequent after R-IPS $t_{(0)}$ (79.4% ±7.7) and R-IPS $t_{(350)}$ (81.0 ± 6.1%) stimulation than after Sham (86.8 ± 4.7%; $p < 0.01$ vs R-IPS $t_{(0)}$; $p < 0.02$ vs R-IPS $t_{(350)}$) (Fig. 7*b*). Similarly to the main experiment, there was an overall significant effect of target validity (RTs: valid, 554 ± 42 ms; invalid, 619 ± 40 ms; $F_{(1,7)} = 6.91$ $p < 0.04$; accuracy: valid, 88.2% correct ± 5.3; invalid, 76.6% correct ± 7.0 $F_{(1,7)} = 7.43$ $p < 0.03$). The results of this control experiment closely replicate the main experiments and demonstrate that the behavioral deficits are not due to impaired sensory encoding of the cue, abnormal directional encoding, or early shifts of attention. Rather they support our interpretation of a deficit of spatial maintenance and selection.

Discussion

Visual deficits after disruption of anticipatory signals in right IPS and FEF

The behavioral deficits, we report, are consistent with the role of the dorsal frontoparietal network in maintaining visual expectations during a delay (Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002; Coull et al., 2003; Serences and Yantis, 2006). It is also consistent with prior studies showing that brief rTMS pulses can cause delayed behavioral effects, in the order of a few seconds as in our experiment (Klimesch et al., 2003).

While previous TMS studies have reported behavioral deficits in stimulus processing and reorienting of attention after interference with prefrontal and posterior parietal regions (Pascual-Leone et al., 1994; Hilgetag et al., 2001; Rushworth et al., 2001; Grosbras and Paus, 2002, 2003; Chambers et al., 2004; Taylor et al., 2005; Thut et al., 2005), this is the first study to report significant behavioral deficits during an anticipatory spatial delay. Another recent study applied rTMS to FEF during spatial cueing, but failed to find a significant disruption on target processing (Taylor et al., 2005).

The impairment of target discrimination was bilateral, i.e., involved both visual fields. This suggests that anticipatory activity in FEF and IPS in this task did not reflect only spatial selection (trial-by-trial cue location), but also, potentially, temporal (the onset of the target 2 s later) and feature expectancies (the shape and orientation of the target) that were also important for the

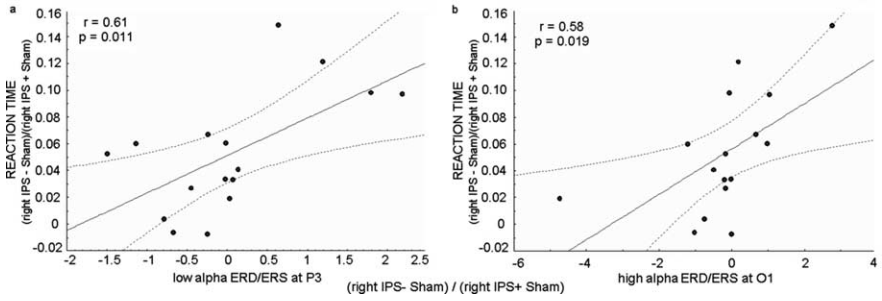

Figure 5. Across-subject correlation between alpha ERD/ERS and RTs. ***a***, Scatter-plot showing the (positive) linear correlation between anticipatory low alpha ERD/ERS at P3 electrode and reaction time, for right "IPS" condition normalized with Sham condition. ***b***, Scatter-plot showing the (positive) linear correlation between anticipatory high alpha ERD/ERS at O1 electrode and reaction time, for right "IPS" condition normalized with Sham condition.

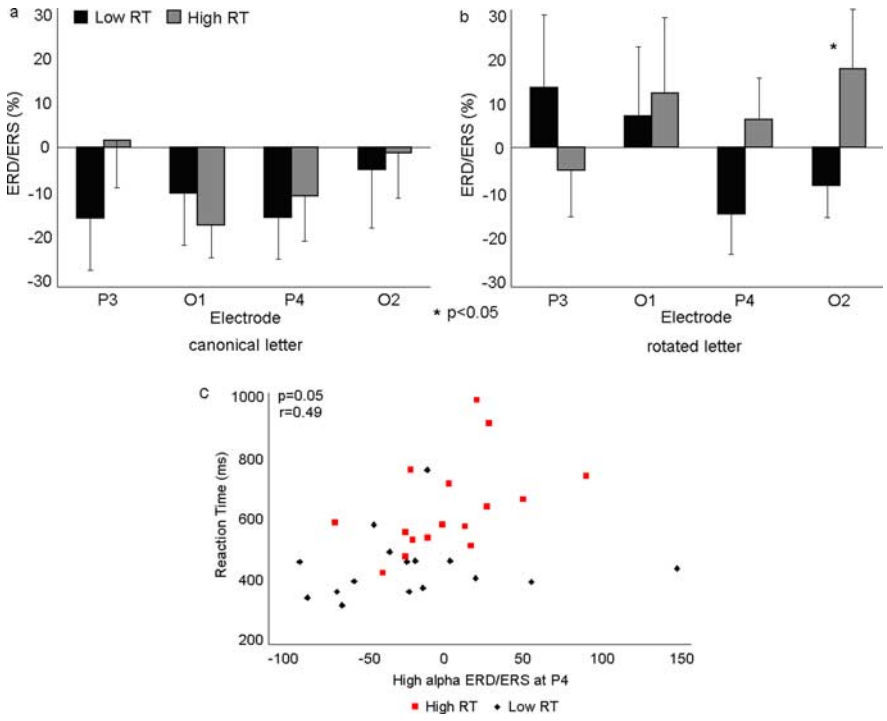

Figure 6. Within-subject relationship between alpha ERD/ERS and RTs. ***a***, Group means (±SE) of the high alpha ERD for the canonical letter divided by reaction time (low or high). ***b***, Group means (±SE) of the high alpha ERD for the rotated letter divided by reaction time (low or high). ***c***, Scatter-plot showing the (positive) linear correlation between anticipatory high alpha ERD/ERS at P4 electrode and high reaction time (red square), for rotated target.

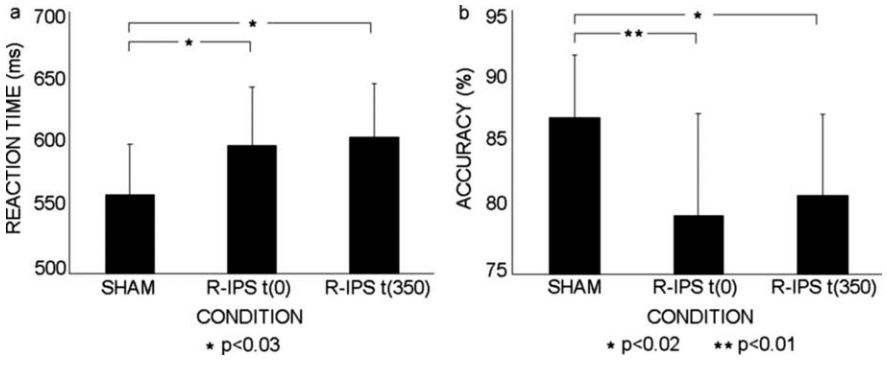

Figure 7. Behavioral effects of rTMS as function of time of stimulation during delay. ***a***, Group means (±SE) of the reaction time (in milliseconds) averaged over target visual field and cue validity. Duncan *post hoc* tests: * $p < 0.03$. ***b***, Group means (±SE) of the accuracy (%).

correct completion of the task. Time- and feature-based selection recruit the frontoparietal network bilaterally (Kanwisher and Driver, 1992; Coull, 2004; Sylvester et al., 2008), albeit with some functional specialization (Giesbrecht et al., 2003; Coull, 2004; Slagter et al., 2007). Alternatively, neuroimaging studies of anticipatory endogenous spatial attention, as in this experiment, have clearly shown that preparatory activity in prefrontal and posterior parietal cortex is bilateral (Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002; Serences and Yantis, 2006), and that regions containing topographic specific signals are relatively small, like "small islands in a sea" of bilateral responses (Jack et al., 2007). Given the size of higher-order parietal and frontal regions is within the spatial radius of rTMS inactivation (<1 cm^2), it is really not surprising that both spatial and nonspatial selective subregions were affected.

Nonetheless, some behavioral effects were spatially selective consistent with the trial-to-trial cueing of location. Behavioral deficits were stronger when targets occurred at unexpected locations, presumably reflecting the importance of IPS and FEF in redirecting spatial attention as previously shown (Pascual-Leone et al., 1994; Hilgetag et al., 2001; Rushworth et al., 2001; Grosbras and Paus, 2002, 2003; Chambers et al., 2004). And, as later discussed, some physiological effects were also spatially selective (see below).

Finally, when compared vis-à-vis the right precentral region (PrCe), our behavioral and physiological effects support a division of labor and functional segregation between a dorsal attention network, including right FEF and IPS, specialized in directing endogenous spatial attention, and a ventral attention network, including right PrCe, not recruited by endogenous shifts but recruited, as shown in other studies, by target processing and stimulus-driven reorienting (Corbetta and Shulman, 2002; Corbetta et al., 2008). This separation, originally proposed on the basis of fMRI activation studies, has been recently strengthened by fMRI connectivity studies in healthy subjects (Fox et al., 2006), fMRI studies of stroke patients with spatial neglect (Corbetta et al., 2005; He et al., 2007), and now inactivation studies with rTMS (this study).

Control of visual attention and alpha desynchronization of occipital rhythms

The most important result of this study is the establishment of a three-way link between anticipatory activity in prefrontal

and parietal cortex during spatial attention, behavioral deficits following rTMS interference, and secondary disruption of anticipatory alpha rhythms in occipital cortex. This three-way relationship is supported by three main findings. First, rTMS on right IPS disrupted the desynchronization of anticipatory (prestimulus) alpha rhythms in parieto-occipital cortex. Second, rTMS on both right IPS and right FEF disrupted the spatially selective topography of alpha power in occipital cortex (Worden et al., 2000; Yamagishi et al., 2003; Sauseng et al., 2005; Thut et al., 2006). Third, the degree of paradoxical alpha synchronization caused by right FEF- and right IPS-rTMS correlated, across- and within-subjects, with behavioral deficits in target discrimination.

The parieto-occipital alpha is the strongest cortical EEG rhythm and is profoundly modulated by attention. Although the generators are not known, alpha power is most consistently localized to the parieto-occipital cortex (Vanni et al., 1997) as in our study (Fig. 3). This has been recently confirmed by MEG studies (Donner et al., 2007; Siegel et al., 2007). Spontaneous oscillations of alpha power have been also recently related to the excitability of occipital cortex to visual stimuli (Romei et al., 2008).

When attention is directed to a spatial location, alpha EEG rhythms in parieto-occipital cortex desynchronize, and lateralize with a stronger modulation contralateral to the locus of attention. The gradient of occipital alpha desynchronization correlates with focusing of spatial attention, and suppression of stimuli at ignored locations (Worden et al., 2000; Sauseng et al., 2005; Thut et al., 2006). It also predicts trial-by-trial the locus of attention and speed of visual perception (Thut et al., 2006). Interestingly, this interhemispheric EEG alpha power gradient is highly reminiscent of anticipatory BOLD signal changes recorded in occipital cortex with fMRI during the allocation of spatial attention, which also show a functionally significant gradient of anticipatory activity (Sestieri et al., 2008; Sylvester et al., 2007, 2008).

Here, we show for the first time that interference with right FEF and IPS anticipatory activity during a spatial delay disrupts the normal alpha desynchronization, and its spatially selective topography in parieto-occipital cortex. Moreover, the paradoxically induced alpha synchronization was functionally significant across- and within-subjects as it correlated with response times to target stimuli. Subjects or trials in which the synchronization was stronger resulted in slower RTs.

These novel results suggest that behavioral deficits caused by rTMS interference of anticipatory activity in FEF and IPS is, at least partly, mediated by disruption of anticipatory alpha rhythms, which previous studies have related to spatial selection in the occipital lobe. We also show that the behavioral impairment reflects a problem of selection, rather than a deficit of perception given the lack of any modulation of sensory evoked potentials (P1, N1). The control experiment shows that the behavioral deficits do not reflect problems with sensory analysis of the cue, encoding of the direction, or early shifts of attention. Of note, using shorter cue-target intervals two previous studies reported modulation of sensory evoked activity after right FEF-rTMS (Fuggetta et al., 2006; Taylor et al., 2007). Both studies reported significant changes in visually evoked activity consistent with top-down interference from parietal and prefrontal cortex on target processing in visual cortex.

The disruptive effects of frontal or parietal rTMS on ongoing EEG occipital rhythms cannot be explained by the induction of local oscillatory activity given the distance between the stimulation and recording sites, and the duration of the effects prolonging nearly 1.5 s after the end of the rTMS train. The most likely explanation is that rTMS disrupted neural signals generated during spatial attention in frontoparietal cortex, which in turn interfered with ongoing oscillations in the occipital lobe. Within the limited spatial resolution of EEG recordings, our results directly show such top-down interaction between control and sensory regions. Top-down effects of control regions onto sensory areas are often postulated, but only recently there has been direct support for this idea. Several studies have shown that electric or magnetic stimulation of FEF (or IPS) induce neural changes in visual cortex (Moore and Armstrong, 2003; Ruff et al., 2006, 2008; Ekstrom et al., 2008). One recent fMRI study reports in physiological conditions, i.e., not during stimulation, that BOLD signal time series in IPS and FEF predict signal time series in occipital cortex, consistent with top-down influences from higher-order to visual regions during anticipatory spatial attention (Bressler et al., 2008).

Our results provide a potential neural mechanism through which such top-down interaction may occur. Attention signals from frontoparietal regions may take control of visual neurons though synchronization. At the local level, i.e., either individual areas or groups of neurons, it is known that attention has a powerful effect on synchronization of neural activity, especially at higher frequencies. Several studies have reported spike-triggered increases in gamma coherence during object selection and spatial attention (Fries et al., 2001; Bichot et al., 2005; Womelsdorf et al., 2006). Gamma coherence modulations can also occur before visual stimulation and be predictive of performance (Womelsdorf et al., 2006). Recent evidence indicates that attention-induced modulation of gamma coherence can be observed across multiple visual areas (V1, V2, V4), and that they occur predominantly in the superficial layers of cortex. Interestingly, parallel changes occur at lower frequencies (alpha and beta bands) in deeper layers of cortex (Robert Desimone, personal communication). These low frequency changes may correspond to the modulations recorded with EEG or MEG. Our findings show that anticipatory alpha rhythms in parieto-occipital cortex, one of the local mechanisms of attention-related neural synchronization, are controlled by top-down signals from IPS and FEF, and that their disruption leads to a suboptimal state of neural synchronization that delays target processing.

Conclusions

To our knowledge, this is the first experiment that directly links the control of spatial attention by frontal and parietal cortex with anticipatory alpha rhythms in occipital cortex. This study underscores the importance of oscillatory neural activity in linking widely separate neuronal populations (Engel et al., 2001; Fries, 2005) during cognitive functions like spatial attention that require a dynamic interaction between cognitive systems for control and areas specialized in sensory analysis.

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