Differential Contribution of Right and Left Parietal Cortex to the Control of Spatial Attention: A Simultaneous EEG–rTMS Study

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We have recently shown that interference with repetitive transcranial magnetic stimulation (rTMS) of right posterior intraparietal sulcus (IPS) cortex during the allocation of spatial attention leads to abnormal desynchronization of anticipatory (pretarget) electroencephalographic alpha rhythms (8–12 Hz) in occipital-parietal cortex and the detection of subsequently presented visual targets (Capotosto et al. 2009). Since lesion data suggest that lesions of the right frontoparietal cortices produce more severe and long-lasting deficits of visual spatial attention than lesions of the left hemisphere, here, we used the mentioned rTMS-electroencephalographic procedure to test if the control of anticipatory alpha rhythms by IPS is asymmetrically organized in the 2 hemispheres. Results showed that interference with either left or right IPS during covert spatial attention equally disrupted the normally lateralized anticipatory modulation of occipital visual cortex, with stronger alpha desynchronization contralaterally to the attended visual field. In contrast, only interference with right IPS induced a paradoxical pretarget synchronization of alpha rhythms and bilateral deficits of target identification. These results suggest that the control of spatial topography of anticipatory alpha rhythms in occipital-parietal cortex is shared between left and right IPS cortex, but that right IPS uniquely contributes to a bilateral prestimulus activation of occipital visual cortex.

Keywords: alpha rhythms, EEG, rTMS, visual cortex, visuospatial attention

Introduction

Frontal and parietal cortices may jointly play an important role in the causal top-down control of spatial attention by funneling anticipatory biases onto sensory representations (Kastner and Ungerleider 2000; Corbetta and Shulman 2002; Serences and Yantis 2006). Direct evidence for this conclusion comes from a variety of sources including electrical microstimulation experiments in monkeys (Moore and Armstrong 2003) and transcranial magnetic stimulation (TMS) studies in humans in combination with either functional magnetic resonance (Ruff et al. 2008, 2009) or electroencephalography (EEG; Capotosto et al. 2009).

A putative physiological mechanism of spatial attention control is the synchronization of oscillatory activity across neural populations in visual cortex (Engel et al. 2001; Fries 2005). A marker of this mechanism is the modulation of EEG alpha rhythms (8–12 Hz), which reflects the synchronization of cortical pyramidal neurons due to signals conveyed by circuits encompassing brainstem, thalamus, and cerebral cortex (Pfurtscheller and Lopes da Silva 1999). The power of parietooccipital alpha rhythms is highest during restful wakefulness and is reduced bilaterally during expectancy and encoding of visual targets

(Klimesch et al. 1998; Worden et al. 2000; Yamagishi et al. 2003; Sauseng et al. 2005; Thut et al. 2006) or events of other modalities (Babiloni et al. 2004, 2008; Babiloni, Brancucci, et al. 2006). However, a contralateral hemispheric preponderance of alpha desynchronization is observed when subjects covertly pay attention to a location in the visual hemifield (Worden et al. 2000; Sauseng et al. 2005). Furthermore, the balance of alpha power between occipital lobes predicts the locus of attention trial-by-trial (Thut et al. 2006). These findings indicate that the contralateral modulation of alpha desynchronization is a neural correlate of the allocation of spatial attention in visual cortex.

We have recently shown that right posterior intraparietal sulcus (IPS), a core region of the so called dorsal attention network (Corbetta and Shulman 2002; Corbetta et al. 2008), putatively involved in the control of spatial attention, is one of the cortical regions that causally controls the anticipatory modulation of alpha rhythms in occipitoparietal cortex (Capotosto et al. 2009). In fact, interference with right IPS activity by rTMS during a preparatory delay, in which subjects covertly directed spatial attention to a peripheral location in expectation of a target, produced an abnormal synchronization and disruption of contralateral alpha power modulation, as well as a bilateral impairment of visual target discrimination.

Here, we test if the control of anticipatory alpha rhythms during spatial attention is asymmetrically organized in the 2 hemispheres. While the right hemisphere dominance for attention in humans is well established based on lesion evidence, it is not known what component of attention is lateralized and the physiological mechanism at the basis of such behavioral lateralization. Some theories have proposed an asymmetry in the hemispheric control of spatial attention (Kinsbourne 1977; Mesulam 1981; Heilman et al. 1985), while other theories have emphasized the dominance of the right hemisphere for nonspatial aspects of attention including arousal, sustained attention, and reorienting (Heilman et al. 1985; Husain and Rorden 2003; Corbetta and Shulman 2011). The former set of theories predicts that the balance of alpha power should be asymmetrical influenced by interference with left or right posterior parietal preparatory activity, while the latter predicts a stronger role of right IPS in the modulation of anticipatory alpha power bilaterally in occipitoparietal cortex.

Materials and Methods

Subjects

Fifteen right-handed (Edinburgh Inventory) healthy adult volunteers (age range: 22–31 years old; 8 females) with no previous psychiatric or

neurological history participated in the 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. Eight subjects in this group were part of a control experiment in a previous study (Capotosto et al. 2009).

Experimental Task

All measurements were carried out at the Institute of Technology and Advanced Bioimaging (ITAB) by the first author (P.C.). The experimental paradigm is shown in Figure 1*a*. Subjects were seated in a comfortable reclining armchair and kept their hands resting on the keyboard of a computer. They maintained fixation on a small white cross stimulus (subtending 0.7° of visual angle) displayed on a black background in the center of a computer screen positioned at a distance of 80 cm. Each trial began with the presentation of a cue stimulus (a small white-filled rectangle subtending about 0.2° visual angle and overlapping either the left or right horizontal segment of the fixation cross) for 100 ms duration that indicated randomly (50%) either a left or a right side location along the horizontal meridian. Following a 2-s stimulus onset asynchrony, a target letter, either L or T (each with 50% probability), was presented for 70 ms at the left or right location at 0.7° of visual angle from the fixation point. The letters were presented in their canonical upright orientation (50% of trials) or rotated 180° 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 location opposite the cue (invalid trials) (Posner 1980). Immediately after the target stimulus, a mask stimulus (130 ms duration) formed by all the possible line segments in the letter stimuli L or T was flashed to interrupt stimulus processing. Subjects were instructed 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) for the letter T (upright or rotated) and a right keyboard button (key L) for the letter L (upright or rotated). The assignment of “target” stimulus (T or L) to the specific key for response (A or L) was counterbalanced across subjects. This arrangement insured that the central cue did not provide any information about the response to execute but only information about the location of the stimulus. This is important to ensure that preparatory processes were visuospatial in origin and not motor related (Broadbent 1971). Reaction times (RTs) 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 employed repetitive TMS (rTMS). The stimulation was delivered through a focal, figure 8 coil (outer diameter of each wing 7 cm), connected with a standard Mag-Stim Rapid 2 stimulator (maximum output 2.2 T). 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; Rossi et al. 2009).

The experimental design included 5 conditions, applied in different blocks, and randomized across subjects. Each subject performed all the conditions. In the “Sham” condition, the stimulation was delivered at the scalp vertex with the position of the coil reversed with respect to the scalp surface, such that the magnetic flux was dispersed in the air. In the 4 active conditions, rTMS interfered with activity at the predetermined scalp sites since we placed the anterior end of the junction of the 2 coil wings. A mechanical arm maintained the handle of the coil angled at about 45° away from the midline (The exact position was adjusted based on the results of the online neuronavigation such that the center of the coil wing was oriented perpendicularly to the point to be stimulated in order to deliver the maximum power.). The center of the coil wings was positioned at a position on the scalp corresponding to 2 cortical regions in the atlas of Talairach and Tournoux (1988) obtained from a meta-analysis of spatial attention studies (He et al. 2007): right pIPS (x, y, z 23, -65, 48) and left IPS (x, y, z -25, -63, 47) (Fig. 1*b*). The right pIPS location is the same as in the study by Capotosto et al. (2009). The location of stimulation was automatically identified on each subject's scalp using the SofTactic navigator system (E.M.S. Italy, www.emsmedical.net). The procedure involves the computation of an estimated volume of head magnetic resonance images (MRIs) in subjects for whom MRIs are unavailable. The estimated MRIs, referred to the Talairach space, are calculated by means of a warping procedure, operating on a template MRI volume on the basis of a set of about 30 points digitized from the subjects scalp. The digitized points are used to compute a subsequent set of reference points which are analogous to a set of points prelocalized on the scalp of the template. The warping procedure is performed using these 2 corresponding sets of reference points. This strategy has been successful in previous rTMS studies of posterior parietal cortex and visuospatial attention (Babiloni, Vecchio, et al. 2006; Harris et al. 2008; Capotosto et al. 2009; Oliveri et al. 2010). At each site (left or right IPS),

Figure 1. Task and rTMS localization. (*a*) Sequence of events during a trial. (*b*) MRI-constructed stereotaxic template showing the sagittal (*a*), coronal (*b*), and axial (*c*) projections of the 2 rTMS sites on the right and left hemisphere.

the stimulation was delivered at 2 intervals: either at onset (t_0) or at 350 ms after the onset of the cue stimulus (t_{350}). This manipulation was introduced to ensure that the effects of rTMS were not related to abnormal cue stimulus encoding but truly reflected modulation of delay activity between cue and target stimuli.

EEG Recordings

To assess the physiological impact of rTMS on anticipatory (delay) alpha rhythms, we recorded simultaneously EEG activity from the scalp. Specifically, we measured the effect of rTMS at different cortical loci on the desynchronization of alpha rhythms in parietooccipital cortex, a reliable physiological correlate of anticipatory spatial attention processes (Worden et al. 2000; Yamagishi et al. 2003; Sauseng et al. 2005; Thut et al. 2006).

EEG data were recorded (BrainAmp; band-pass, 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 below 5 k Ω . The artifact of rTMS on the EEG activity lasted about 10 ms and did not generate any alteration in the power spectrum (Supplementary Fig. 1a). 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. About 120 EEG trials were collected for each condition 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 100 (± 15).

Computation of the Event-Related Desynchronization/Synchronization

For the EEG spectral analysis, 2 subbands of alpha rhythms were used, namely low- and high-frequency alpha. These subbands were determined in accordance 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. Several control analyses focused on other frequency bands such as beta and gamma. In particular, with respect to the individual beta peak (IBP), low-frequency beta ranged from 2 Hz before IBP to IBP, high-frequency beta ranged from IBP to 2 Hz after IBP, and the gamma band ranged from 35 to 40 Hz. The EEG power spectrum analysis was based on an fast fourier transform (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 rhythms was obtained using the following standard formula (Pfurtscheller and Lopez da Silva 1999):

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

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. 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 1 to 2 s after the cue stimulus. Of note, although in our previous study, we used postcue window between $+0.5$ and $+1.5$ s, here, we choose a period from 1 to 2 s to avoid a time window too close to the end of one of the active conditions (t_{350}). Topographic maps of the alpha ERD/ERS were calculated in the period following the cue stimulus and rTMS stimulation (from 1 to 2 s postcue onset). The maps were represented on the standard T_1 mean brain template (152 subjects; statistical parametric mapping—SPM96 Brain Imaging Center of the Montreal Neurological Institute) by a spline interpolating function.

Statistical Analysis

Statistical comparisons were performed by analyses of variance (ANOVAs) for repeated measures. We used a Mauchley’s test to evaluate the sphericity assumption of the ANOVA, a Greenhouse-Geisser procedure for the correction of the degrees of freedom based, and Duncan tests for post hoc comparisons (alpha, $P < 0.05$).

For the EEG analysis, we carried out a first analysis on alpha ERD/ERS at electrodes P3, P4, O1, O2, separately for low and high alpha subbands, with Condition (sham, R-IPS (t_0), L-IPS (t_0)), Cue side (left, right cue), Hemisphere (left (P3, O1), right (P4, O2)), and Electrode of interest (parietal, occipital) as within-subject factors. In this analysis, the left hemisphere (P3 and O1 electrodes) is ipsilateral to L-IPS and contralateral to R-IPS (vice versa for the right hemisphere). Next, to examine the effect of rTMS on the normally lateralized anticipatory desynchronization of alpha rhythms in parietooccipital electrodes, that is, stronger contralaterally to the side of spatial attention, we ran an ANOVA for each Condition (sham, R-IPS (t_0), L-IPS (t_0)), using the alpha ERD/ERS, separately for low and high alpha subbands, respectively, as dependent variable and Stimulus (right or left cue stimulus), Hemisphere (contralateral, ipsilateral to the cue stimulus), and Electrode of interest (parietal or occipital) as within-subject factors. In this analysis, contralateral hemisphere electrodes included left hemisphere electrodes (P3, O1) for right cues and right hemisphere electrodes (P4, O2) for left cues (the opposite for ipsilateral hemisphere electrodes).

For the analysis of the behavioral effects, we used RT and percentage of correct responses (Hits) to the target stimuli as function of Condition (sham, R-IPS (t_0), L-IPS (t_0)), target side (left, right), and target validity (valid, invalid) as within-subject factors.

Finally, to test for significant relationships between electrophysiological measures of attention control and visual performance, we computed a correlation analysis (Pearson test, $P < 0.05$) between alpha ERD/ERS during the cue period and RTs to valid target stimuli. For this analysis, alpha ERD/ERS values in electrodes ipsilateral to the spatial cue were subtracted from alpha ERD/ERS in electrodes contralateral to the spatial cue for each experimental condition (Sham, R-IPS (t_0), L-IPS (t_0)). This interhemispheric alpha ERD/ERS measure was then correlated to RTs to stimuli in the attended visual field (valid trials). For example, RTs for right valid targets were correlated with the difference between alpha ERD/ERS at P3 (left hemisphere, contralateral to attention) minus P4 (right hemisphere, ipsilateral to attention) for the 3 experimental conditions. The 2 alpha subbands were considered separately (i.e., low- and high-frequency). This analysis is based on the results of several EEG studies that find a correlation between the locus of spatial attention and the interhemispheric balance of alpha power (Thut et al. 2006; Siegel et al. 2008).

Several control analyses were carried out.

An ANOVA was conducted in the beta, separately for low and high beta subbands and gamma bands ERD/ERS, as dependent variable, with Condition (sham, R-IPS (t_0), L-IPS (t_0)), Cue side (left, right cue), Hemisphere (left, right), and Electrode of interest (parietal, occipital) as within-subject factors. In addition, for beta, separately for low and high subbands and gamma bands a correlation analysis (Pearson test, $P < 0.05$) was computed between ERD/ERS during the cue period and RTs to valid target stimuli.

To test whether the timing of rTMS, either at the onset of the cue stimulus (t_0) or after a delay (t_{350}), produced a different EEG modulation, we ran ANOVAs on the ERD/ERS, after subtracting sham ERD/ERS, separately in the low and high alpha subbands with Condition (Right IPS or Left IPS), Time of stimulation (rTMS (t_0) or rTMS (t_{350})), Electrode of interest (parietal or occipital), and Hemisphere (left (P3, O1), right (P4, O2)) as within-subject factors. ANOVAs were also run on the behavioral data (RTs, hits) with Condition (R-IPS, L-IPS), Time of stimulation (t_0 , t_{350}), Cue side (left, right cue), and Validity (valid, invalid) as within-subject factors. The influence of timing on alpha ERD/ERS topography was evaluated with an ANOVA with Condition (R-IPS (t_0), L-IPS (t_0), R-IPS (t_{350}), L-IPS (t_{350})), and Hemisphere (contralateral, ipsilateral to the cue stimulus), and Electrode of interest (parietal, occipital) as within-subject factors.

A third set of control analyses examined the effect of rTMS during the cue period on the stimulus-evoked potential. ANOVAs compared

the size of the early sensory evoked components (P1/N1) across conditions for valid trials. Unfortunately, there were not 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.

Finally, to rule out effects of rTMS on baseline alpha power, an ANOVA with condition (Sham, R-IPS (t0), L-IPS (t0)), electrode of interest (parietal or occipital), and hemisphere (right or left hemisphere) as factors compared power changes, separately for low- and high-frequency alpha subbands, in the period preceding the cue that was used to calculate the rest power of the aforementioned ERD/ERS formula.

Results

Pre-target Electroencephalography

The EEG signals chosen for the analysis of alpha rhythms (+1 to +2 s after cue onset) were free of rTMS artifacts. The alpha frequency peak was clearly recognizable at all electrodes of interest and the mean IAF peak across subjects was 10.4 Hz (± 0.3 standard error, SE) for each condition (Supplementary Fig. 1b).

For illustrative purpose, Figure 2a shows the topography of parietooccipital alpha ERD/ERS in the 3 rTMS conditions (Sham, R-IPS (t0), L-IPS (t0)) during the delay period and before target presentation. During Sham, we observed a diffuse ERD (desynchronization) at both low- and high-frequency alpha subbands in parietal-occipital cortex. A similar distribution of anticipatory alpha ERD was observed during left IPS (t0) rTMS, albeit weaker, especially on the left hemisphere ipsilateral to the

site of stimulation. In contrast, R-IPS (t0) rTMS completely abolished the normal anticipatory alpha ERD, which was substituted by a paradoxical and bilateral increment of alpha power (synchronization, ERS), especially on the right hemisphere ipsilateral to the site of stimulation. These qualitative observations were confirmed by quantitative analyses. For the low-frequency alpha ERD/ERS, the ANOVA showed a significant main effect of Condition ($F_{2,28} = 3.84$, $P < 0.04$), that was accounted for by an overall greater anticipatory alpha power (ERS) for R-IPS (t0) than Sham condition ($P < 0.02$) (Fig. 2b). The same effect was observed for the high-frequency alpha ERD/ERS ($F_{2,28} = 7.86$, $P < 0.002$) with greater anticipatory alpha ERS for R-IPS (t0) than Sham ($P < 0.001$) or L-IPS (t0) ($P < 0.02$) (Fig. 2c). There was also a significant interaction of Condition by Hemisphere ($F_{2,28} = 5.79$, $P < 0.01$) indicating a stronger modulation in the hemisphere ipsilateral to stimulation.

Next, we examined whether R-IPS or L-IPS rTMS modified the spatially selective topography of alpha desynchronization in parietooccipital cortex (Worden et al. 2000; Yamagishi et al. 2003; Sauseng et al. 2005; Thut et al. 2006). As expected, anticipatory alpha ERD in the high-frequency subband was stronger over the hemisphere contralateral to the side of attention during Sham ($F_{1,14} = 4.46$, $P = 0.053$) (Fig. 3). This asymmetrical hemispheric topography was completely disorganized by rTMS over both R-IPS (t0) and L-IPS (t0) (Fig. 4), irrespective of the side of attention.

Notably, the above EEG modulations were independent of the timing of rTMS (t0 vs. t350). A stronger anticipatory alpha power (ERS) was observed for R-IPS than L-IPS, for both low-frequency alpha ERD/ERS ($F_{1,14} = 6.06$, $P < 0.03$) and high-frequency alpha ERD/ERS ($F_{1,14} = 7.75$, $P < 0.02$), irrespective of whether rTMS was delivered simultaneously with the cue stimulus or 350 ms later during the delay (Supplementary Fig. 2). Moreover, for the high-frequency alpha ERD/ERS, there was also a significant interaction of Condition by Hemisphere ($F_{1,14} = 5.49$, $P < 0.04$) indicating a stronger modulation in the hemisphere ipsilateral to stimulation. Moreover, the disruption of alpha ERD/ERS topography was independent of the timing of stimulation (Supplementary Fig. 3) and of the side of attention.

In summary, interference with right, but not left, IPS activity, during the covert allocation (t0) or maintenance (t350) of

Figure 2. Topography of alpha power as function of rTMS conditions. (a) Topographic maps (rear view) of anticipatory low and high alpha ERD/ERS during the cue period (+1000 to 2000 ms after the onset of the cue). (b) Group means ($\pm$ SE) of the low alpha ERD/ERS divided by hemisphere (left or right). (c) Group means ($\pm$ SE) of the high alpha ERD/ERS divided by hemisphere (left or right). Duncan post hoc tests: 1 ($P < 0.02$) or 2 asterisks ($P < 0.001$).

Figure 3. Contralateral spatial selectivity of alpha power by rTMS condition. Group means ($\pm$ SE) of the high alpha ERD/ERS for the 3 Conditions (Sham, R-IPS (t0), L-IPS (t0)) divided by Hemisphere (contra or ipsi to cue stimulus).

Figure 4. Behavioral effects of rTMS at different cortical sites. (a) Group means ($\pm$ SE) of the RT (ms). (b) Group means ($\pm$ SE) of the accuracy (%). Duncan post hoc tests: 1 ($P < 0.05$) asterisk. (c) The accuracy of visual discrimination was significantly more impaired on invalid trials after rTMS in R-IPS (t0) than Sham and L-IPS (t0). Duncan post hoc tests: 1 asterisk ($P < 0.0001$).

visuospatial attention, resulted in a paradoxical and bilateral synchronization of alpha rhythms in parietooccipital cortex. However, both left and right IPS interferences caused a disruption of alpha power spatial topography in parietooccipital cortex during covert visuospatial attention.

Behavior target processing

Figure 4 plots the behavioral effects of rTMS on visual target identification during Sham, right or left IPS conditions. Repetitive TMS was delivered for 150 ms after the onset of a central cue stimulus (100 ms duration), covertly directing attention to a left or right location, while the target was briefly presented ~ 2 s later. There was a significant main effect of rTMS conditions on both RTs ($F_{2,28} = 3.42$, $P < 0.05$) and accuracy ($F_{2,28} = 3.54$, $P < 0.05$). RTs were significantly slower after both R-IPS (t0) (592 ± 24 ms) and L-IPS (t0) (587 ± 23 ms) as compared with Sham (557 ± 21 ms; both $P < 0.05$) (Fig. 4a). In addition, R-IPS significantly impaired response accuracy in both visual fields ($85.6 \pm 3.1\%$) when compared with both Sham ($89.9 \pm 2.2\%$) and L-IPS rTMS ($90.6 \pm 1.5\%$) (both $P < 0.05$) (Fig. 4b).

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, $556 \text{ ms} \pm 42$; invalid, $603 \text{ ms} \pm 45$; $F_{1,14} = 11.02$, $P < 0.005$; accuracy: valid, $91.4\% \text{ correct} \pm 3.8$; invalid, $84.6\% \text{ correct} \pm 5.0$; $F_{1,14} = 14.35$, $P < 0.002$). However, the decrement in accuracy after right IPS interference was especially severe for targets presented at unattended locations as indicated by a significant interaction of Condition by Validity on accuracy ($F_{2,28} = 3.64$, $P < 0.04$; post hocs: R-IPS (t0) vs. L-IPS (t0), $P < 0.0001$; vs. Sham, $P < 0.0001$)

(Fig. 4c). Of note, a similar interaction was not observed for RTs ($P = 0.4$). Finally, as in our previous experiment (Capotosto et al. 2009), RTs for targets presented in the left visual field were slower than RTs for targets presented in the right visual field (left VF: 586 ± 23 ms; right VF: 571 ± 23 ms, $F_{1,14} = 7.68$, $P < 0.02$). This difference likely reflects the well-known superiority of the right visual field (left hemisphere) for alphabetical material (Rizzolatti et al. 1971).

The behavioral deficit was independent of whether the stimulation was delivered simultaneously with or 350 ms after the onset of the cue stimulus (Supplementary Fig. 4). This results rules out that the observed behavioral deficits reflect abnormal encoding of the central spatial cue.

In summary, interference with right, but not left, IPS activity, during the covert allocation (t0) or maintenance (t350) of visuospatial attention, impaired the identification of subsequently presented visual shapes in both visual fields, especially when stimuli were presented at unexpected locations. Response times were slowed down by parietal TMS irrespective of the hemisphere of stimulation.

Behavior/EEG Correlation

To test for the functional significance of anticipatory alpha power topography, we examined the correlation between interhemispheric differences in ERD/ERS and visual performance (RTs to attended visual targets). No correlation was found in the Sham condition. However, in the L-IPS (t0) condition, there was a positive correlation between RTs to valid targets in the right visual field and the interhemispheric (contra minus ipsi) ERD/ERS difference at the parietal electrode (i.e., P3 minus P4) for the high alpha frequency ($r = 0.74$, $P < 0.002$) (Fig. 5a). A similar trend was also observed with rTMS over the R-IPS (t0) ($r = 0.50$, $P = 0.058$) (Fig. 5b). No significant correlation was obtained when correlating interhemispheric alpha ERD/ERS with RTs to left visual field targets. Hence, stronger disruption after left (and right) rTMS of the interhemispheric ERD/ERS difference in left occipitoparietal cortex correlated with slower responses to targets in the right visual field.

Control Analyses

Control analyses were run on the beta, separately for low and high beta subbands and gamma ERD/ERS, respectively. Both beta and gamma bands showed higher synchronization ipsilaterally to the side of stimulation (Supplementary Fig. 5), as shown by a significant interaction between Condition and Hemisphere for low beta ERD/ERS ($F_{2,28} = 5.40$, $P < 0.01$), high beta ERD/ERS ($F_{2,28} = 8.16$, $P < 0.002$), and gamma ERD/ERS ($F_{2,28} = 9.06$, $P < 0.001$). This result is similar to what observed in the high-frequency alpha ERD/ERS. Interestingly, however, the abnormal and bilateral occipitoparietal synchronization observed in the alpha band after right IPS-rTMS was not observed in the beta and gamma bands. Moreover, a lower overall desynchronization for both right and left IPS (t0) conditions was observed in gamma as compared with Sham condition ($F_{2,28} = 4.23$, $P < 0.03$). Finally, in the L-IPS (t0) condition, there was a positive correlation between RTs to valid targets in the right visual field and the interhemispheric (contra minus ipsi) ERD/ERS difference at the parietal electrode (i.e., P3 minus P4) for the low beta frequency ($r = 0.73$, $P < 0.002$) (Supplementary Fig. 6a) and for high beta frequency ($r = 0.66$, $P < 0.006$) (Supplementary Fig. 6b). No

Figure 5. Across-subject correlation between alpha ERD/ERS and RTs. (a) Scatter plot showing the (positive) linear correlation between anticipatory high alpha ERD/ERS at parietal electrode (i.e., P3–P4) and RT to valid target presented in the right hemifield, for left “IPS” condition. (b) Scatter plot showing the (positive) linear correlation between anticipatory high alpha ERD/ERS at parietal electrode (i.e., P3–P4) and RT to valid target presented in the right hemifield, for right “IPS” condition.

correlation was found in the gamma band. In summary, while both left and right IPS interference seem to cause a relative decrement of ipsilateral desynchronization in alpha, beta, and gamma bands, only right IPS interference leads to a paradoxical bilateral synchronization of alpha rhythms.

As in our previous work (Capotosto et al. 2009), parietal TMS affected preparatory processes, not target evoked activity. Early visual components evoked by the target stimulus (P1, N1) were compared across conditions in the occipital and parietal electrodes. The amplitude and latency of the P1–N1 complex were not affected by rTMS during the cue period in any of the conditions ($P > 0.9$, Supplementary Fig. 7). Accordingly visual discrimination deficits were likely not related to impaired target processing but disrupted selection.

Finally, none of our results could be explained by a change of alpha power during the baseline period before the cue onset (see Materials and Methods). This result was confirmed for both low- and high-frequency alpha subbands ($P > 0.5$ in both cases).

Discussion

Combined rTMS–EEG methods were used to study the causal role of left versus right posterior parietal cortex in the control of anticipatory EEG rhythms in occipitoparietal cortex during visuospatial attention. Behaviorally, rTMS interference over right IPS cortex caused bilateral deficits of visual discrimination more severe for targets presented at unattended locations. This deficit was not observed after left IPS interference. Neurally, both left and right IPS–rTMS caused a disruption of the normal contralateral (to the side of attention) preponderance of anticipatory alpha desynchronization in occipitoparietal cortex. Notably, however, only right IPS interference caused a paradoxical bilateral synchronization of alpha rhythms in parietooccipital cortex. This latter effect was specific to the alpha band. This study therefore isolates 2 separate physiological effects of posterior parietal interference onto occipital alpha rhythms during spatial attention: a spatially selective modulation, contributed to by both left and right posterior parietal cortex, and a more bilateral nonspatial modulation exclusively controlled by right posterior parietal cortex.

Spatial Modulation of Alpha Rhythms by Posterior Parietal Cortex

When attending to a peripheral location in the visual field, many studies have shown a modulation of the topography of alpha rhythms in occipitoparietal cortex, with a stronger desynchronization or decrease of alpha power contralaterally to the attended location. This mechanism has been correlated with the allocation of spatial attention in the visual field (Thut et al. 2006; Siegel et al. 2008). Here, we show that interference with either left or right IPS activity leads to a disruption of occipital alpha topography. Results for right IPS replicate those obtained in our previous study (Capotosto et al. 2009).

These findings are consistent with the notion that both left and right posterior parietal regions contribute in the top-down control of the locus of spatial attention, in contrast to theories positing a right hemisphere dominance for coding and/or directing attention to both visual fields (Mesulam 1981, 1999; Heilman et al. 1985). Specifically, that the balance of interhemispheric activity in dorsal frontoparietal cortex codes for the locus of spatial attention is supported by many lines of evidence. First, many areas in posterior parietal (and frontal) cortex contain retinotopic maps of contralateral space (Sereno et al. 2001; for a recent review, see Silver and Kastner 2009). Nearly in all mapping studies, no hemispheric asymmetries have been detected either in the topographic extent or in the strength of spatially selective activity in the 2 hemispheres. The only exception is a recent study by Szczepanski et al. (2010) who found spatially selective activity region in right superior parietal lobule with no counterpart in the left hemisphere. Second, based on predictive analysis of preparatory activity during spatial attention, the best predictor of the locus of attention in higher order frontal and posterior parietal regions, and visual cortex, is a relative gradient of activity across maps in the 2 hemispheres (Bisley and Goldberg 2003; Sylvester et al. 2007; Siegel et al. 2008). Third, top-down influences during spatial attention onto visual cortex originate from both left and right visual cortex (Bressler et al. 2008).

Our TMS findings suggest that interference with either left or right IPS preparatory activity during the allocation of spatial attention leads to disruption of topographically selective changes in alpha power in the occipital lobe. Interestingly, this top-down disruptive modulation seemed to be directed to

both occipital visual cortices. In fact, interference with preparatory activity in either parietal cortex led to disruption of occipital alpha topography irrespective of whether spatial attention was directed to the contralateral or ipsilateral visual field to the stimulated hemisphere.

It is appealing to hypothesize that interhemispheric gradients of preparatory activity in left and right posterior parietal (frontal) maps feedback onto visual cortex during the allocation of spatial attention leading to alpha power asymmetries. Asymmetry in alpha power across left and right occipital cortex is predictive on a trial-by-trial basis of the locus of attention (Thut et al. 2006; Siegel et al. 2008). These EEG changes in alpha power are paralleled by interhemispheric gradients of blood oxygen level-dependent (BOLD)-functional MRI (fMRI) preparatory activity during spatial attention in occipital cortex that are also predictive of the locus of attention (Sylvester et al. 2007, 2008, 2009). These similarities suggest a potential link between EEG and BOLD signal preparatory changes, which is supported by increasing evidence for a link between oscillations of the local field potential, including those in the alpha frequency range and BOLD signals (Mantini et al. 2007; Goense and Logothetis 2008; Nir et al. 2008; He and Raichle 2009; de Pasquale et al. 2010). Moreover, recent single unit studies have emphasized a link between modulation of slow frequencies (<17 Hz in Womelsdorf et al. 2006; <5 Hz in Mitchell et al. 2007; 2009) and spatial attention.

Right IPS and Bilateral Desynchronization of Occipital Cortex

In contrast to the symmetrical contribution of left and right IPS in modulating the topography of parietooccipital alpha power, we found a dominant role of right IPS in the anticipatory bilateral desynchronization of occipital cortex prior to target presentation. Interference with right IPS activity led to a paradoxical alpha synchronization in both left and right occipital cortices. Interestingly, this bilateral synchronization was specific to alpha and did not extend to beta or gamma frequencies.

These findings suggest that right parietal cortex plays a dominant role in the bilateral desynchronization, that is, activation of occipital cortex in preparation of visual events. This result resonates with an asymmetry found by Ruff et al. (2008, 2009) in a combined TMS/fMRI in which stimulation of right but not left posterior parietal cortex causes bilateral changes of fMRI activity bilaterally in the occipital lobe. Ruff et al. (2009) also reported hemispheric asymmetries in FEF, as well as a functional differentiation between parietal and frontal sites. In our previous study (Capotosto et al. 2009), we also found a functional difference between right IPS and right FEF in the same visuospatial paradigm. While interference with preparatory activity at both sites led to a disruption of anticipatory alpha power in parietooccipital cortex, similar to what observed for left and right IPS in this experiment, only interference with right IPS caused a paradoxical synchronization bilaterally in parietooccipital cortex. While a full design comparing within the same subject, the effect of left and right IPS versus left and right FEF during visuospatial attention would be ideal, dose limitations and relative low signal-to-noise of TMS-EEG methods make such experiment difficult to perform.

What is the physiological function of alpha desynchronization? Spontaneous fluctuations of occipital-parietal alpha power have been recently linked to the conscious perception of spatial cue stimuli (Babiloni, Vecchio, et al. 2006), as well as with

excitability of occipital cortex and subjective perception of TMS-induced phosphenes (Romei et al. 2008). Interestingly, the fluctuations in alpha power relevant to phosphene perception were location specific but did not resemble the characteristic asymmetrical topography observed during directed spatial attention (Romei et al. 2008). Our current results extend these findings by showing that right, but not left, posterior parietal cortex plays a role in controlling the overall excitability of visual cortex before stimulus appearance, possibly by suppressing the fluctuation of occipital-parietal alpha oscillations.

This physiological role would be consistent with the putative dominant role of the right hemisphere in regulating the level of global cortical activation (Heilman and Van Den Abell 1979), specifically of right posterior parietal cortex in the regulation of vigilance (Paus et al. 1997). The dominant influence of right hemisphere mechanisms on cortical arousal may depend on corticofugal pathways from polymodal areas like IPS (Pandya and Kuypers 1969) onto thalamic/reticular formation mechanisms. Accordingly, stimulation of the mesencephalic reticular formation (MRF) causes strong desynchronization of the EEG via midline thalamic nuclei (Moruzzi and Magoun 1949) and lesions in both MRF and medial thalamus on the right side lead to profound sensory neglect (Reeves and Hagamen 1971; Watson et al. 1974). There is also growing evidence for ascending cholinergic pathways playing an activating role in cortical alpha rhythms and information processing (Holschneider et al. 1997; Suffczynski et al. 2001; Babiloni et al. 2009, 2010).

Interference with Parietal Preparatory Processes during Visuospatial Attention and Deficits of Target Identification

The relationship between behavioral performance and EEG modulation is complex. The observed bilateral deficit in visual shape identification, especially for targets presented at unattended locations, after rTMS interference to right IPS cortex during a preparatory spatial attention delay, replicates our previous work (Capotosto et al. 2009). Here, we also show that interference with left IPS causes a delay in response time (comparable to one observed for right IPS) but no deficit in visual discrimination.

Lack of spatial specificity, that is, similar deficits for targets contralateral and ipsilateral to right IPS-rTMS, suggests that the deficit may not be related to an abnormal allocation of spatial attention, but an overall decreased responsiveness, which in turn could be associated with the bilateral disruption of alpha desynchronization. In Capotosto et al. (2009), we reported a significant correlation between individual variability in relative synchronization induced by right parietal TMS and visual RTs across visual fields. That correlation was not replicated in this group of subjects, but it is highly significant (Pearson $r = 0.46$, $P < 0.01$) when we combine data across experiments ($N = 31$).

The disproportionate effect on invalidly cued trials may indicate that the interference effect extended beyond the cue delay into the target period. Interference with right IPS activity at the time of detection of an invalid target may have affected visual reorienting processes consistent with previous TMS evidence (Pascual-Leone et al. 1994; Hilgetag et al. 2001; Rushworth et al. 2001; Grosbras and Paus 2002, 2003; Chambers et al. 2004) and neuroimaging evidence of a selective recruitment of right parietal cortex during stimulus-driven reorienting (Corbetta and Shulman 2002; Shulman et al. 2009).

Finally, the significant correlation between interhemispheric ERD/ERS and RTs to targets in the right visual field, confirmed for both left and right IPS stimulation in this experiment and for right IPS when collapsing data across this, and Capotosto et al. (2009) ($r = 0.42$, $P < 0.02$) suggest a preferential role of left parietal cortex in preparatory processes for alpha-numeric characters. This effect may suggest the importance of alpha anticipatory modulations in feature-like attention anticipatory processes.

Conclusions

This study shows a predominant role of right human parietal cortex in the non spatial activation of occipital cortex in anticipation of visual stimuli. In contrast, the topography of alpha power in occipital cortex during spatial attention is regulated by feedback signals from both left and right parietal cortices.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

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Notes

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