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# Electrophysiological Correlates of Stimulus-driven Reorienting Deficits after Interference with Right Parietal Cortex during a Spatial Attention Task: A TMS-EEG Study

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## Abstract

■ TMS interference over right intraparietal sulcus (IPS) causally disrupts behaviorally and EEG rhythmic correlates of endogenous spatial orienting before visual target presentation [Capotosto, P., Babiloni, C., Romani, G. L., & Corbetta, M. Differential contribution of right and left parietal cortex to the control of spatial attention: A simultaneous EEG-rTMS study. *Cerebral Cortex*, 22, 446–454, 2012; Capotosto, P., Babiloni, C., Romani, G. L., & Corbetta, M. Fronto-parietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. *Journal of Neuroscience*, 29, 5863–5872, 2009]. Here we combine data from our previous studies to examine whether right parietal TMS during spatial orienting also impairs stimulus-driven reorienting or the ability to efficiently process unattended stimuli, that is, stimuli outside the current focus of attention. Healthy volunteers ( $n = 24$ ) performed a Posner spatial cueing task while their EEG activity was being monitored. Repetitive TMS (rTMS) was applied

for 150 msec simultaneously to the presentation of a central arrow directing spatial attention to the location of an upcoming visual target. Right IPS-rTMS impaired target detection, especially for stimuli presented at unattended locations; it also caused a modulation of the amplitude of parieto-occipital positive ERPs peaking at about 480 msec (P3) post-target. The P3 significantly decreased for unattended targets and significantly increased for attended targets after right IPS-rTMS as compared with sham stimulation. Similar effects were obtained for left IPS stimulation albeit in a smaller group of volunteers. We conclude that disruption of anticipatory processes in right IPS has prolonged effects that persist during target processing. The P3 decrement may reflect interference with postdecision processes that are part of stimulus-driven reorienting. Right IPS is a node of functional interaction between endogenous spatial orienting and stimulus-driven reorienting processes in human vision. ■

## INTRODUCTION

Visual attention defines the psychological and neural processes that facilitate processing of behaviorally relevant sensory information. Posner and colleagues developed many years ago a simple RT paradigm to study the mental operations of spatial attention (Posner, 1980). In one version of the task, subjects are cued to covertly direct their attention to a peripheral location by a central symbolic cue (an arrow) that correctly predicts the target location in the majority of trials (e.g., 80% of the times). In the minority of trials, the cue incorrectly predicts the target location (e.g., 20% of trials). Targets presented at validly cued locations or valid targets are typically responded to faster than targets presented at invalidly cued location or invalid targets, and the RT difference is thought to index the time necessary to reorient attention from a currently

attended to a novel location of interest (Posner, 1980). Such a process is defined as “stimulus-driven reorienting” (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002).

The modulation of visual sensory processing by spatial cueing, as in the Posner task, has been studied by examining ERPs to (frequent) valid and (rare) invalid stimuli (Eimer, 1993; Mangun & Hillyard, 1991). The relative ERP components are classified according to their scalp topography, positive (P) or negative (N) polarity, and timing or order of appearance. Visual targets elicit early positive and negative parieto-occipital cortex ERP components (P1, N1) that are greater in amplitude at attended (validly cued targets) than unattended locations (invalidly cued targets; Mangun & Hillyard, 1991). In contrast, a late positive ERP component (i.e., P3) shows larger amplitude to invalidly than validly cued targets (Eimer, 1996; Mangun & Hillyard, 1991). This late modulation is consistent with the characteristic strong ERP positivity (i.e., P3 or P300) associated with the presentation of infrequent targets and motor reactions in “oddball” paradigms (Hruby & Marsalek, 2003;

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Polich & Comerchero, 2003). Although the exact processes associated with P3 responses is a hotly debated issue beyond the purpose of this report, in the context of a spatial cueing task P3 modulation by targets at unattended location is a convenient physiological marker of a reorienting response that includes both spatial (e.g., a shift of attention) and nonspatial (e.g., changes in arousal, reward, or task set) processes associated with infrequent events.

From a neuroanatomical point of view, the control of spatial attention has been localized to a set of dorsal frontoparietal regions, including cortex along the intraparietal sulcus (IPS), thought to send top-down biasing signals to sensory regions in anticipation of stimulus processing (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Corbetta & Shulman, 2002). Recent evidence indicates a direct causal role of posterior parietal cortex on attention-related modulation of visual cortex activity (Capotosto, Babiloni, Romani, & Corbetta, 2009, 2012; Ruff et al., 2009). For instance, repetitive TMS (rTMS) interference of IPS cortex during the allocation of spatial attention produces disruption of anticipatory (pretarget) EEG desynchronization of alpha rhythms (about 8–12 Hz) in occipito-parietal cortex, especially in the hemisphere contralateral to the locus of attention (Capotosto et al., 2009, 2012). These findings are consistent with a causal role of IPS cortex in the anticipatory and endogenous allocation of spatial attention.

Here, we test whether IPS cortex also plays a causal role in stimulus-driven reorienting and its neurophysiological correlates. In previous studies, we observed that right IPS-rTMS during the endogenous allocation of spatial attention had lingering effects on target detection producing identification deficits especially for targets presented at unattended locations (Capotosto et al., 2009, 2012). This suggests an interaction between right IPS anticipatory processes and stimulus-driven reorienting. In this study we consider the neurophysiological correlates of this behavioral deficit in stimulus-driven re-orienting (Corbetta et al., 2008).

We hypothesize that interference with anticipatory activity in right parietal cortex will produce greater abnormalities of late positive ERP component (i.e., P3) of the visually evoked response to invalid targets (Hruby & Marsalek, 2003; Polich & Comerchero, 2003). This component is consistently modulated during oddball paradigms that, similar to invalidly cued spatial targets in the Posner paradigm, involve the detection of a behaviorally relevant low-frequency event. Furthermore, theoretical and empirical evidence suggest a link between stimulus-driven reorienting and P3 (Corbetta et al., 2008; Nieuwenhuis, Aston-Jones, & Cohen, 2005). To address this issue, we combined EEG data from our two previous experiments and analyzed visual ERPs for either validly cued or invalidly cued visual targets to determine whether TMS interference over right IPS mainly affects amplitude of parietal P3 following unattended (i.e., rare, invalid) as compared with attended (frequent, valid) visual targets.

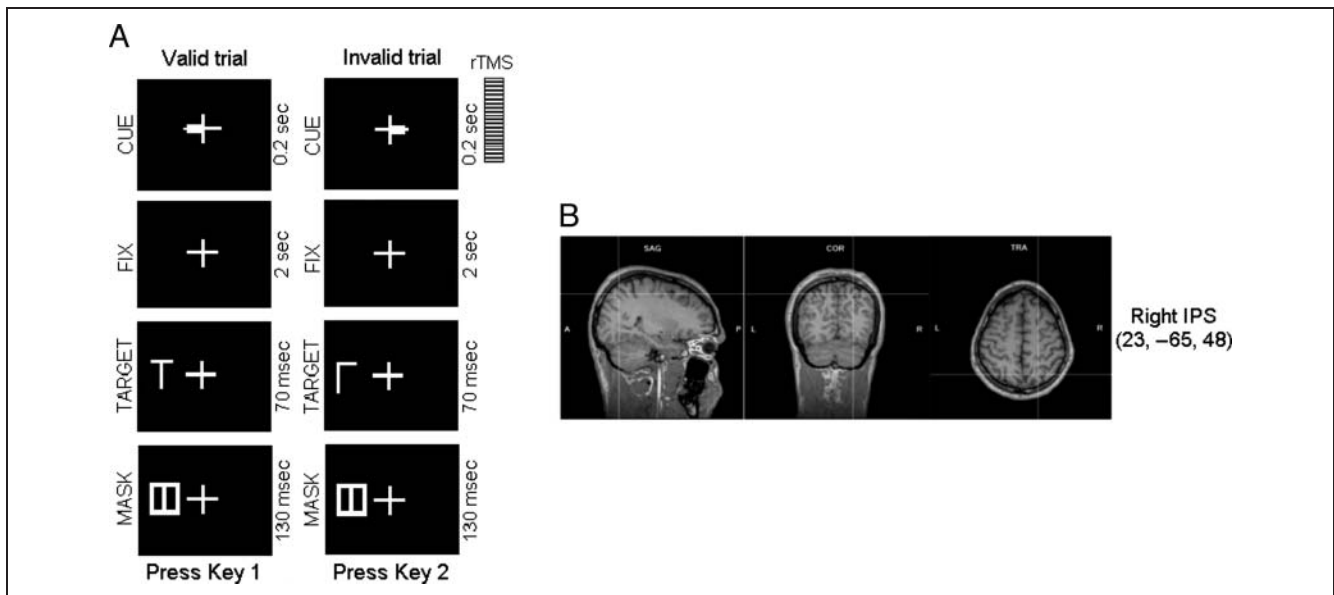
## METHODS

### Participants

Twenty-four right-handed (Edinburgh Inventory) healthy adult volunteers (age range = 22–31 years old; 14 women) with no previous psychiatric or neurological history participated in the experiments as described in our previous publications. 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 were established by the University of Chieti Institutional Review Board and Ethics Committee.

### Experimental Task

All measurements were carried out at the Institute of Technology and Advanced Bioimaging by the first author (P. C.). The experimental paradigm is shown in Figure 1A. The participants 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  $0.7^\circ$  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  $0.2^\circ$  visual angle and overlapping either the left or right horizontal segment of the fixation cross) for 200-msec duration that indicated randomly (50%) either a left or right side location along the horizontal meridian. Following a 2-sec SOA, a target letter, either L or T (each with 50% probability), was presented for 70 msec at the left or right location at  $0.7^\circ$  visual angle from the fixation point. The letters were presented in their canonical upright orientation (50% of trials) or rotated  $180^\circ$  along the vertical axis (the other 50%). Both letters had a diameter of  $0.7^\circ$  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 msec 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



**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 active rTMS site.

(Broadbent, 1971). 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 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 T). Individual resting excitability threshold for right motor cortex stimulation was preliminarily determined by following standardized procedure (Rossi et al., 2001; Rossini et al., 1994). The rTMS train was delivered at the onset of the cue stimulus based on the following parameters: 150 msec 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 (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Anderson et al., 2006; Machii, Cohen, Ramos-Estebanez, & Pascual-Leone, 2006; Wassermann, 1998).

The experimental design included two conditions, applied in different blocks, and randomized across subjects. Each participant 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 active condition, rTMS interfered with activity at the predetermined scalp sites because we placed the anterior end of the junction of the two 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 on-line neuro-

navigation such that the center of the coil wing was oriented perpendicularly to the point to be stimulated to deliver the maximum power). The center of the coil wings was positioned at a position on the scalp corresponding to the cortical region 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; Figure 1B). The right IPS location is the same as in the studies by Capotosto and colleagues (2009, 2012), in which the TMS coil was positioned on individual basis, taking into account subject's scalp shape. The location of stimulation was automatically identified on each subject's scalp using the SofTatic navigator system (E.M.S. Italy, www.emsmedical.net). The procedure involves the computation of an estimated volume of head MRIs in patients for whom MRIs are unavailable (i.e., all participants in this study). 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 40 points digitized from the subjects scalp. The digitized points are used to compute a subsequent set of reference points that are analogous to a set of points pre-localized on the scalp of the template. The warping procedure is performed using these two corresponding sets of reference points. This strategy has been successful in previous rTMS studies of posterior parietal cortex and visuospatial attention (Oliveri et al., 2010; Capotosto et al., 2009; Harris, Benito, Ruzzoli, & Miniussi, 2008; Babiloni, Vecchio, Miriello, Romani, & Rossini, 2006).

### EEG Recordings

EEG data were recorded (BrainAmp, Brain Products GmbH, Munich, Germany; 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 below 5 k $\Omega$ . The artifact of rTMS on the EEG activity lasted about 10 msec. For the analysis, we filtered between 0.1 and 40 Hz. Two electro-oculographic channels were used to monitor eye movement and blinking. The acquisition time for all data was set from  $-2$  to  $+2$  sec after cue stimulus. About 120 EEG trials were collected for each condition and for each subject. The EEG single trials were 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 re-referenced 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.

As the analysis was focused on the difference in P3 between invalidly and validly cued targets, a major challenge was the low percentage (20%) of invalidly cued targets presented to each participant. This low number of trials was further decreased by the rejection of EEG segments containing artifacts or recorded during incorrect trials. In the end, the mean number of invalid trials for the sham and right IPS condition was  $19.7 (\pm 0.5 SE)$  and  $17.4 (\pm 0.7 SE)$ , respectively. Even if low, this number was adequate for the planned analysis. In fact robust P3 ERP components can be obtained by averaging a small number of event-related EEG segments as compared with other components of ERPs or EPs (i.e., N1 or P1). This is because of P3's high amplitude and broad shape, which allows for an effective summation of the voltages across the EEG segments (low jitter effect). Accordingly, several previous EEG studies have recognized and measured P3 waveform even in single EEG segments, as for example in the case of brain computer interface applications (D'Avanzo, Schiff, Amodio, & Sparacino, 2011; Zou, Zhang, Yang, & Zhou, 2010).

### Analysis of ERPs Components

For the two conditions (sham and right IPS), the artifact-free EEG trials were averaged with respect to the onset of the visual target stimuli (zero time) to generate two classes of ERPs. The first class was constituted by EEG trials related to the valid target stimuli, whereas the second class was formed by EEG trials related to the invalid target stimuli. To avoid any artifact introduced by the stimulation in the baseline period, the peaks amplitude of the P3 component were calculated with reference to a baseline taken in a period preceding the rTMS from 0.5 sec before the cue onset. The latency and amplitude of P3 peak, typically maximal over centroparietal recording sites, was measured at Pz electrode, in agreement with most literature on this topic. In particular, the P3 peak latency was defined as the instant showing the maximum amplitude of the late positive ERPs in the range from  $+300$  msec to  $+600$  msec.

Moreover, we also investigated the P2 component, usually associated with the detection of salient features of targets with respect to distracters across feature dimensions such as color, size, and space (Akyürek, Leszczyński, & Schubö, 2010; Eimer & Kiss, 2008; O'Donnell, Swearer, Smith, Hokama, & McCarley, 1997). The P2 peak was defined as the positive peak at Pz electrode preceding the P3 peak.

The maps were represented on a 3-D template cortical model by a spline interpolating function. This model is based on the magnetic resonance data of 152 subjects digitized at the Brain Imaging Center of the Montreal Neurological Institute (SPM96; Figure 3).

### Statistical Analysis

Statistical comparisons were performed by ANOVAs for repeated measures. We used a Mauchly'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 ( $p < .05$ ).

For the analysis of the behavioral effects, we used RT and percentage of correct responses (Hits) to the target stimuli as a function of Condition (sham, right IPS), Target side (left, right), and Target validity (valid, invalid) as within-subject factors. For the ERPs analysis, we tested the hypothesis that the amplitude of scalp P3 peak was different in the two experimental conditions (sham, right IPS). To this aim, we carried out a statistical analysis (ANOVA) for the P3 amplitude peak measured at Pz electrode as a function of Condition (sham, right IPS) and Target validity (valid, invalid) as within-subject factors. Moreover, we performed a similar statistical analysis for the P2 amplitude peak. Furthermore, we carried out a statistical analysis (ANOVA) comparing the P3 latency peak measured at Pz electrode as a function of Condition (sham, right IPS) and Target validity (valid, invalid) taken as within-subject factors. The same statistical design was used for P2 latency peak.

Finally, to examine possible effect of target and electrode laterality, we carried out two analyses only for valid targets. The first statistical analysis (ANOVA) was on the P3 amplitude peak measured at Pz electrode as a function of Condition (sham, right IPS) and Target side (left, right) as within-subject factors. The second statistical analysis (ANOVA) was on the P3 amplitude peak measured at parietal lateralized electrodes (P7, P8) as a function of Condition (sham, right IPS), Target side (left, right), and Electrode (ipsilateral or contralateral to the target stimulus) as within-subject factors.

## RESULTS

### Behavior

The first analysis confirmed in a larger group of subjects ( $n = 24$ ) behavioral observations of target identification

deficits after right IPS-rTMS as reported in our publications (Capotosto et al., 2009, 2012). The train of rTMS was delivered for 150 msec simultaneously with the onset of a central cue stimulus (200-msec duration) covertly directing attention to a left or right location, whereas the target was briefly presented ~2 sec later. There was a significant main effect of rTMS condition (sham, right IPS) on both RTs,  $F(1, 23) = 16.1$ ;  $p < .0005$ , and accuracy,  $F(1, 23) = 21.7$ ;  $p < .0001$ . RTs were significantly slower after the right IPS ( $567 \pm 23$  msec) as compared with sham ( $526 \pm 22$  msec). In addition, the right IPS significantly impaired response accuracy in both visual fields ( $84.8 \pm 1.9\%$ ) when compared with sham ( $89.4 \pm 1.5\%$ ).

rTMS did not disrupt the observers' ability to direct spatial attention to the target location as indicated by a significant main effect of Target validity (RTs: valid,  $520 \pm 23$  msec; invalid,  $573 \pm 23$  msec,  $F(1, 23) = 18.10$   $p < .0003$ ; accuracy: valid,  $89.8 \pm 1.6\%$  correct; invalid,  $84.3 \pm 1.7\%$  correct,  $F(1, 23) = 12.65$   $p < .002$ ). 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  $\times$  Target validity on accuracy,  $F(1, 23) = 4.70$   $p < .04$ , and by relevant post hoc tests (right IPS vs. sham for valid trials,  $p < .02$ ; right IPS vs. sham for invalid trials,  $p < .0002$ ; Figure 2C). Finally, as in our previous experiments (Capotosto et al., 2009, 2012), the effect of active and pseudo-rTMS was not differential for left or right visual field targets. However, targets presented in the right visual field were identified more accurately and rapidly than targets presented in the left visual field as indicated by a significant main effect of Target side (left visual field:  $553 \pm 23$  msec; right

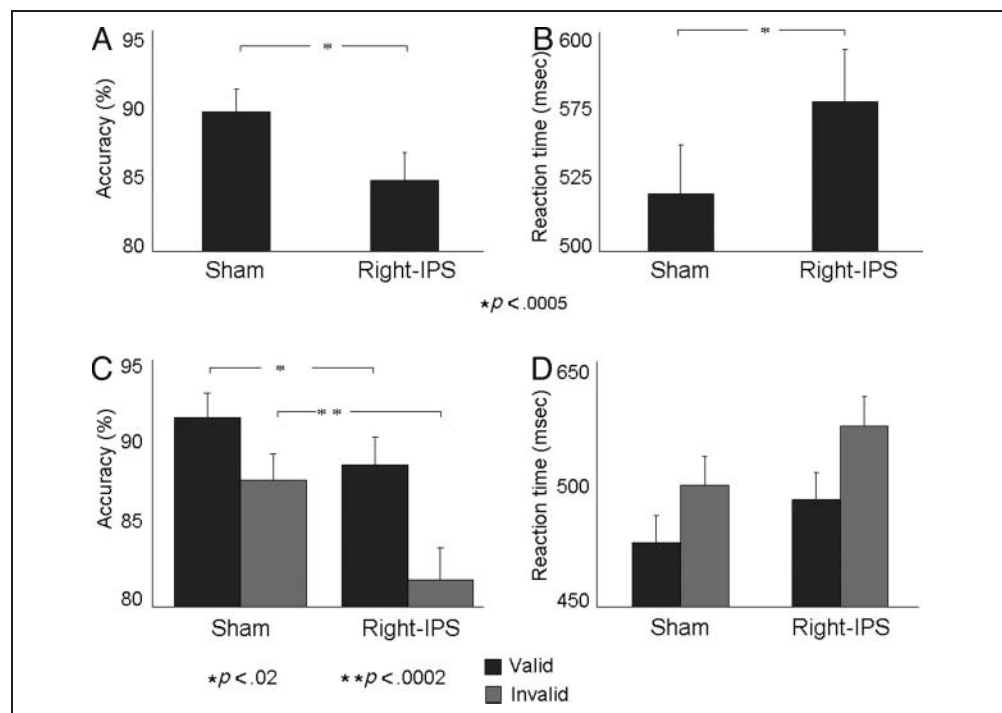
visual field:  $532 \pm 23$  msec,  $F(1, 23) = 21.4$   $p < .0001$ ; accuracy: left visual field:  $85.1 \pm 2.2\%$  correct; right visual field:  $89.0 \pm 1.7\%$  correct,  $F(1, 23) = 7.48$   $p < .02$ ). This difference likely reflects the well-known superiority of the right visual field (left hemisphere) for alphabetical material (Rizzolatti, Umiltà, & Berlucchi, 1971).

## EEG

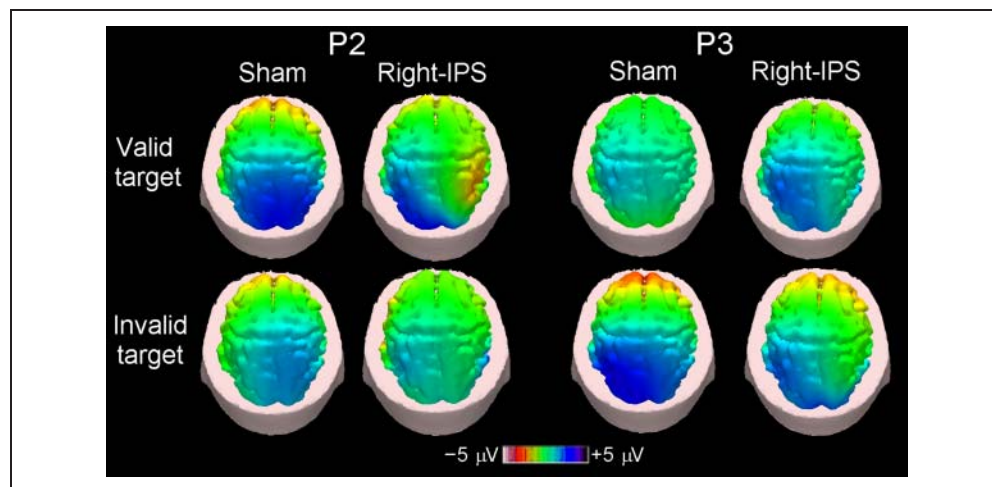
Figure 3 shows the grand average map across subjects ( $n = 24$ ) of P2 and P3 peak amplitudes in the two conditions (sham, right IPS) for valid and invalid trials, separately. Qualitatively, during both experimental conditions, valid targets produced a larger P2. On the contrary, only for the sham condition, invalid targets produced a larger P3 response. Right IPS stimulation seems to strongly reduce the P3 response to invalid targets. The maximum amplitude of P2 and P3 was bilaterally located in the parietal areas around the electrode Pz.

Figure 4A shows the time evolution of the grand average ( $n = 24$ ) ERP waveforms at Pz electrode in the sham and right IPS conditions separately for valid and invalid targets. The main finding of this study is that the ERPs waveforms at Pz electrode clearly show a reduction of the P3 amplitude on invalid targets after right parietal TMS as compared with sham. The mean latency of the P3 peak was  $+489$  msec ( $\pm 20$  SE) in the sham condition and  $+488$  msec ( $\pm 17$  SE) in the right IPS condition ( $p = .9$ ). An ANOVA on P3 peak amplitude showed the main effect of Target validity,  $F(1, 23) = 8.86$ ;  $p < .007$ , with a stronger overall response to invalid than valid targets. Moreover, interestingly this analysis demonstrated a significant

**Figure 2.** Behavioral effects of rTMS at different cortical sites. (A) Group means ( $\pm SE$ ) of the accuracy (%). (B) Group means ( $\pm SE$ ) of the RT (msec). Duncan post hoc tests:  $*p < .0005$ . (C) The accuracy of visual discrimination was significantly more impaired on invalid trials after rTMS in right IPS than sham. Duncan post hoc tests:  $*p < .02$  or  $**p < .0002$ . (D) The RT of visual discrimination was equally impaired on invalid and valid trials after rTMS in right IPS.



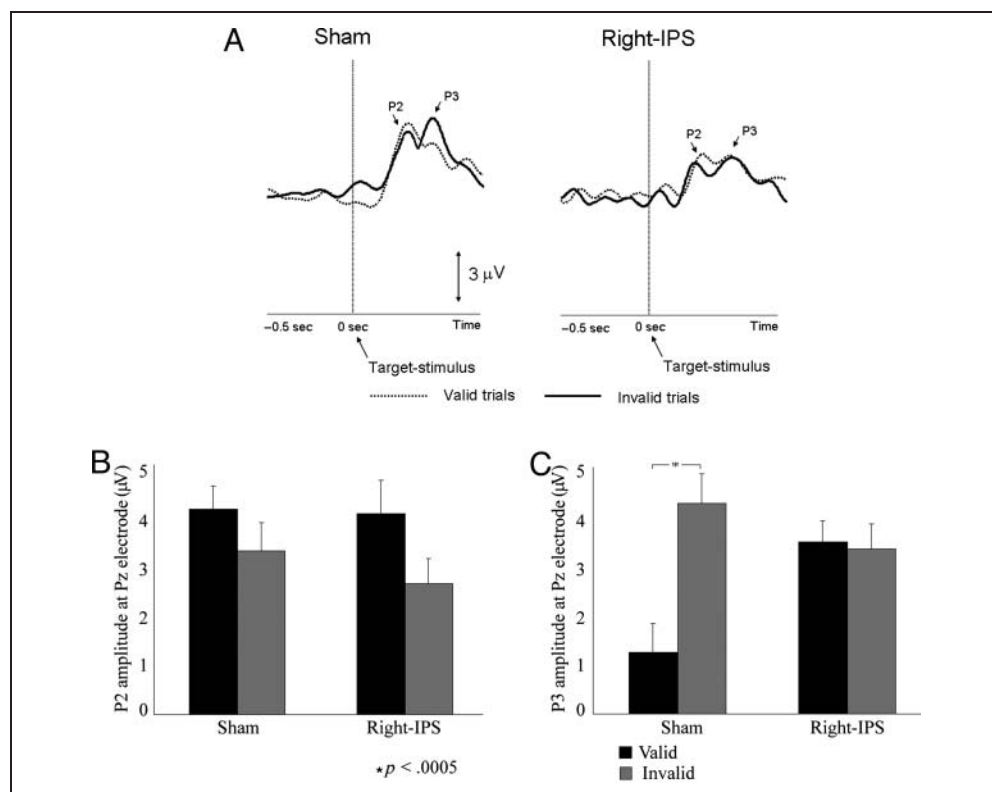
**Figure 3.** Topography of ERPs components as function of rTMS conditions. Topographic maps of P2 and P3 peaks amplitude.



interaction of Condition (sham, right IPS) by Target validity (valid, invalid;  $F(1, 23) = 12.75$ ;  $p < .002$ ; Figure 4C). Post hoc tests confirmed that the difference in P3 amplitude between invalid and valid targets was maintained in the Sham condition ( $p < .0005$ ), but it was lost after right IPS-TMS. Conversely, an ANOVA on P2 peak amplitude only showed the main effect of Target validity,  $F(1, 23) = 13.08$ ;  $p < .002$ , with a stronger overall response to valid than invalid targets, but it was not observed an interaction of Condition (sham, right IPS) by Target validity (valid, invalid; Figure 4B). In summary, interference with right IPS anticipatory (pretarget) activity clearly disrupts only late (P3) target evoked response.

To investigate if left IPS-rTMS stimulation caused similar electrophysiological interference, we analyzed the ERPs waveforms in a subset of subjects (10 of 24) that participated in our previous study (Capotosto et al., 2012). Results showed that the ERP waveforms at Pz electrode after left parietal TMS have a similar trend to that observed after right parietal TMS. Namely, P3 amplitude was strongly reduced on invalid targets. There was no significant difference of Hemisphere overall (left IPS, right IPS;  $p = .73$ ) or interaction of Hemisphere (left IPS, right IPS) by Target validity (valid, invalid;  $p = .17$ ). Finally, comparing left IPS with Sham condition, we also observed a similar interaction of the right IPS. In fact, an ANOVA on P3

**Figure 4.** ERPs waveforms. (A) Grand averaged ( $n = 24$ ) waveforms of ERPs obtained averaging data of all subjects. These ERPs refer to the valid and invalid trials at Pz electrode in the sham and right IPS conditions. (B) Group means ( $\pm SE$ ) of the P2 peak amplitude. (C) Group means ( $\pm SE$ ) of the P3 peak amplitude. Duncan post hoc tests:  $*p < .0005$ .



peak amplitude demonstrated a significant interaction of Condition (sham, left IPS) by Target validity (valid, invalid;  $F(1, 9) = 9.03$ ;  $p < .02$ ). Nevertheless, the restricted number of subjects on which we could run this analysis advises caution on its conclusions.

Finally, no main effects or interactions were observed in both analyses that examined possible effect of target ( $p < .2$ ) and electrode ( $p < .3$ ) laterality.

## DISCUSSION

We show that interference with anticipatory activity in the right IPS during spatial orienting has behavioral and electrophysiological effects on the identification of targets presented outside the current focus of attention. rTMS stimulation (duration = 150 msec, frequency = 20 Hz; intensity at 100% of individual motor threshold) at the beginning of a 2-sec-long cue period during a Posner orienting task impaired target discrimination of alpha-numerical characters at a peripheral location, especially when presented at unattended or invalidly cued locations. In parallel, we observed a change of the normal P3 response with a reduction to unattended targets. Finally, we observed similar effects for left IPS stimulation albeit on a smaller group of subjects.

First, we consider the possible mechanisms through which the P300 response to targets may be affected by IPS-rTMS during the cue period. In previous work, we showed that right IPS stimulation interferes with the normal alpha desynchronization of the parieto-occipital cortex typically observed when subjects direct and maintain covert visuospatial attention to a peripheral location (Capotosto et al., 2009). The alpha desynchronization is thought to represent an inhibitory mechanism that allows synchronization of higher frequencies (e.g., gamma) during visuospatial attention. Gamma coherence is thought to facilitate communication between distant neuronal populations by concentrating spike trains around the peak of the excitability cycle (Fries, 2005).

The presentation of targets causes an evoked response that reflect both a power increase as well as a phase-resetting of ongoing oscillations (Mazaheri & Jensen, 2006). The interference observed around 300–400 msec then indicates interference with the above processes. In electrophysiological recordings with subdural grids from epileptic patients undergoing invasive monitoring for epilepsy, we observed during the Posner orienting task both delta (~2 Hz) phase resetting during the cue period, as well as theta phase resetting to targets across multiple occipital (e.g., MT), parietal (IPS/SPL, TPJ) and prefrontal areas (FEF, VFC). The latency of this theta phase reset is around 300–400 msec comparable with the P300 evoked response. Interestingly this phase modulation was significantly stronger for invalidly cued (unattended) than validly cued (attended) targets. Our current experiment shows that interference with synchronization during the cue period has long-standing (>2 sec) and behaviorally relevant

effects to targets. This could involve a smaller power response or more variable phase resetting to targets through mechanisms such as phase-to-amplitude coupling (Canolty & Knight, 2010) or cross-frequency phase coupling (Jensen & Colgin, 2007). This interpretation, however, does not fit well with the relative normal latency of the P300 after right IPS stimulation and the relative enhancement of the response to valid targets. Still valid targets were impacted by right IPS-rTMS at least behaviorally both in terms of latency and accuracy.

Next, let's consider the interpretation of our findings from a more psychological perspective. Our results show that right IPS is a central core for the control not only of endogenous but also stimulus-driven attention, that is, re-orienting to unattended stimuli (see also the recent TMS study of Chica, Bartolomeo, & Valero-Cabré, 2011). Anatomically, this is consistent with a dual network model of attention derived from fMRI studies in healthy subjects and brain-injured patients with spatial neglect (Corbetta & Shulman, 2002, 2011; Corbetta et al., 2008), in which both right IPS and right TPJ play an important role during spatial re-orienting. Physiologically, the fMRI pattern of response to unattended targets shares many of the physiological features of P300 (P3b) including sensitivity to target behavioral relevance and target frequency, sensory multimodality, and lack of modulation by motor responses (see Corbetta et al., 2008; Nieuwenhuis et al., 2005, for extensive discussions). A localization of P3b to temporo-parietal cortex is also consistent with lesion studies and fMRI studies of P3b (Mantini, Corbetta, Perrucci, Romani, & Del Gratta, 2009; Stevens, Calhoun, & Kiehl, 2005).

The functional significance of P300 remains uncertain. Two main components have been distinguished through oddball paradigms, in which standard frequent stimuli are mixed in with rare targets (two-stimuli oddball) or rare targets and distracters (three-stimuli oddball). Parietal P3b (to targets) has been linked to task relevance and decision-making and may reflect memory context updating processes and/or processing closure (Picton, 1992; Verleger, 1988). Frontocentral P3a (to distracters) is thought to reflect an aspect of the orienting response related to evaluative attention processes (Hruby & Marsalek, 2003; Polich & Comerchero, 2003). According to the context-updating theory of P3 generation, the brain networks generating the P3a and P3b are modulated by overall arousal level, which governs the amount of attention available for task performance (Polich & Comerchero, 2003); the higher the global brain arousal, the higher the P3a and P3b amplitude (Polich & Comerchero, 2003). Our P300 response to invalid targets is analogous to P3b.

The interference produced by right IPS-rTMS on P300 was relatively late latency (300–500 msec), suggesting that parietal P3b does not serve an early orienting response to the unexpected (rare) target locations, as shown by psychophysical estimates of stimulus-driven shifts of attention in the order of 50–100 msec (Corbetta et al., 2008). Rather, it may serve as a post-decision reset function consistent



with update theories of P3 (Polich & Comerchero, 2003; Picton, 1992; Verleger, 1988) and more recent animal models of decision-making (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005). Moreover, it has been noted that deficits induced by rTMS do not reflect a cumulative effect building up over many trials but actually reflect interference with preparatory processes on a trial-by-trial basis (Hamidi, Johson, Feredoes, & Postle, 2011; Capotosto et al., 2009).

The final observation of our study was that right and left IPS stimulation produced similar findings. This is consistent with the notion that IPS is part of a bilateral and symmetrical dorsal attention network involved in the allocation of spatial attention and that bilateral IPS activation is observed during the cue period of the Posner task (Corbetta & Shulman, 2002). Given the small sample size for the comparison ( $n = 10$  participants), this conclusion is preliminary.

## Conclusions

This study shows a causal and temporally limited influence of a magnetic interference on right parietal cortex during cue stimulation on stimulus-driven spatial reorienting and target stimuli discrimination. Specifically, right IPS-rTMS following a spatial cue impairs detection of subsequently presented unattended (rare, invalid) visual targets and correspondingly abolishes the typical difference in amplitude of the parietal P3b between invalid and valid targets, in the period of 300–500 msec poststimulus. The present results suggest that causal interference with anticipatory processes in posterior parietal cortex during the pretarget spatial orienting has prolonged effects (>2 sec later) on stimulus-driven reorienting to unattended visual targets (i.e., P3b). These results directly show a functional interaction between systems for spatial orienting and reorienting of attention (Corbetta et al., 2008; Corbetta & Shulman, 2002) and indicate an important role of IPS for human vision.

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## REFERENCES

Akyürek, E. G., Leszczyński, M., & Schubö, A. (2010). The temporal locus of the interaction between working memory consolidation and the attentional blink. *Psychophysiology*, *47*, 1134–1141.

Anderson, B., Mishory, A., Nahas, Z., Borckardt, J. J., Yamanaka, K., Rastogi, K., et al. (2006). Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. *The Journal of ECT*, *22*, 49–53.

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, *28*, 403–450.

Babiloni, C., Vecchio, F., Miriello, M., Romani, G. L., & Rossini, P. M. (2006). Visuo-spatial consciousness and parieto-occipital areas: A high-resolution EEG study. *Cerebral Cortex*, *16*, 37–46.

Bouret, S., & Sara, S. J. (2005). Network reset: A simplified overarching theory of locus coeruleus noradrenaline function. *Trends in Neurosciences*, *28*, 574–582.

Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2008). Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *Journal of Neuroscience*, *28*, 10056–10061.

Broadbent, D. (1971). The psychological demands of work. *Proceedings of the Royal Society of Medicine*, *64*, 703–707.

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences*, *14*, 506–515.

Capotosto, P., Babiloni, C., Romani, G. L., & Corbetta, M. (2009). Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. *Journal of Neuroscience*, *29*, 5863–5872.

Capotosto, P., Babiloni, C., Romani, G. L., & Corbetta, M. (2012). Differential contribution of right and left parietal cortex to the control of spatial attention: A simultaneous EEG-rTMS study. *Cerebral Cortex*, *22*, 446–454.

Chica, A. B., Bartolomeo, P., & Valero-Cabré, A. (2011). Dorsal and ventral parietal contributions to spatial orienting in the human brain. *Journal of Neuroscience*, *31*, 8143–8149.

Corbetta, C., & Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, *34*, 569–599.

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: From environment to theory of mind. *Neuron*, *58*, 306–324.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*, 201–215.

D'Avanzo, C., Schiff, S., Amodio, P., & Sparacino, G. (2011). A Bayesian method to estimate single-trial event-related potentials with application to the study of the P300 variability. *Journal of Neuroscience Methods*, *198*, 114–124.

Eimer, M. (1993). Spatial cueing, sensory gating and selective response preparation: An ERP study on visuo-spatial orienting. *Electroencephalography and Clinical Neurophysiology*, *88*, 408–420.

Eimer, M. (1996). The N2pc component as an indicator of attentional selectivity. *Electroencephalography and Clinical Neurophysiology*, *99*, 225–234.

Eimer, M., & Kiss, M. (2008). Involuntary attentional capture is determined by task set: Evidence from event-related brain potentials. *Journal of Cognitive Neuroscience*, *20*, 1423–1433.

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, *9*, 474–480.

Hamidi, M., Johson, J. S., Feredoes, E., & Postle, B. R. (2011). Does high-frequency repetitive transcranial magnetic stimulation produce residual and/or cumulative effects within an experimental session? *Brain Topography*, *23*, 355–367.

- Harris, I. M., Benito, C. T., Ruzzoli, M., & Miniussi, C. (2008). Effects of right parietal transcranial magnetic stimulation on object identification and orientation judgments. *Journal of Cognitive Neuroscience*, *20*, 916–926.
- He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron*, *53*, 905–918.
- Hruby, T., & Marsalek, P. (2003). Event-related potentials—The P3 wave. *Acta Neurobiologiae Experimentalis*, *63*, 55–63.
- Jensen, O., & Colgin, L. L. (2007). Cross-frequency coupling between neuronal oscillations. *Trends in Cognitive Sciences*, *11*, 267–269.
- Machii, K., Cohen, D., Ramos-Estebanez, C., & Pascual-Leone, A. (2006). Safety of rTMS to non-motor cortical areas in healthy participants and patients. *Clinical Neurophysiology*, *117*, 455–471.
- Mangun, G. R., & Hillyard, S. A. (1991). Modulations of sensory-evoked brain potentials indicate changes in perceptual processing during visual-spatial priming. *Journal of Experimental Psychology: Human Perception and Performance*, *17*, 1057–1074.
- Mantini, D., Corbetta, M., Perrucci, M. G., Romani, G. L., & Del Gratta, C. (2009). Large-scale brain networks account for sustained and transient activity during target detection. *Neuroimage*, *44*, 265–274.
- Mazaheri, A., & Jensen, O. (2006). Posterior alpha activity is not phase-reset by visual stimuli. *Proceedings of the National Academy of Sciences, U.S.A.*, *103*, 2948–2952.
- Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychological Bulletin*, *131*, 510–532.
- O'Donnell, B. F., Swearer, J. M., Smith, L. T., Hokama, H., & McCarley, R. W. (1997). A topographic study of ERPs elicited by visual feature discrimination. *Brain Topography*, *10*, 133–143.
- Oliveri, M., Zhaoping, L., Mangano, G. R., Turriziani, P., Smirni, D., & Ciolotti, L. (2010). Facilitation of bottom-up feature detection following rTMS-interference of the right parietal cortex. *Neuropsychologia*, *48*, 1003–1010.
- Picton, T. W. (1992). The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology*, *9*, 456–479.
- Polich, J., & Comerchero, M. D. (2003). P3a from visual stimuli: Typicality, task, and topography. *Brain Topography*, *15*, 141–152.
- Posner, M. I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology*, *32*, 3–25.
- Rizzolatti, G., Umiltà, C., & Berlucchi, G. (1971). Opposite superiorities of the right and left cerebral hemispheres in discriminative reaction time to physiognomical and alphabetical material. *Brain*, *94*, 431–442.
- Rossi, S., Cappa, S. F., Babiloni, C., Pasqualetti, P., Miniussi, C., Carducci, F., et al. (2001). Prefrontal cortex in long-term memory: An “interference” approach using magnetic stimulation. *Nature Neuroscience*, *4*, 948–952.
- Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*, 2008–2039.
- Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., et al. (1994). Non invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. *Electroencephalography and Clinical Neurophysiology*, *91*, 79–92.
- Ruff, C. C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Weiskopf, N., & Driver, J. (2009). Hemispheric differences in frontal and parietal influences on human occipital cortex: Direct confirmation with concurrent TMS-fMRI. *Journal of Cognitive Neuroscience*, *21*, 1146–1161.
- Stevens, M. C., Calhoun, V. D., & Kiehl, K. A. (2005). fMRI in an oddball task: Effects of target-to-target interval. *Psychophysiology*, *42*, 636–642.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.
- Verleger, R. (1988). Event-related potentials and cognition: A critique of the context updating hypothesis and an alternative interpretation of P3. *Behavioral and Brain Sciences*, *11*, 343–427.
- Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology*, *108*, 1–16.
- Zou, L., Zhang, Y., Yang, L. T., & Zhou, R. (2010). Single-trial evoked potentials study by combining wavelet denoising and principal component analysis methods. *Journal of Clinical Neurophysiology*, *27*, 17–24.