

Causal Contributions of the Left Frontal Eye Field to Conscious Perception

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The quest for the neural correlates of consciousness has led to controversial results. When contrasting consciously seen versus unseen stimuli, some authors have proposed that consciousness is related to activity in visual areas along the ventral cortical visual stream, while others propose the implication of parietal and frontal regions (Dehaene and Changeux 2011). When invisibility is caused by neglect or inattention, high levels of activity recorded in early visual areas (Vuilleumier et al. 2001) suggest that further activity in fronto-parietal regions might be necessary for conscious perception. Recent functional magnetic resonance imaging evidence (Chica, Paz-Alonso, et al. 2012) suggested a key role for the left frontal eye field (FEF) in the attentional modulation of visual consciousness. Here, we used the high temporal resolution and causal power of event-related transcranial magnetic stimulation to explore the causal contributions of the left FEF on conscious perception and to assess whether or not these effects are mediated by the orienting of spatial attention. Our results provide the first causal evidence on the contribution of the left FEF to conscious visual perception and indicate that such effects are likely to be mediated by its known role on attentional orienting.

Keywords: conscious perception, frontal eye field, spatial attention, transcranial magnetic stimulation

Introduction

Spatial attention has often been considered as an important antecedent of conscious perception (Posner 1994). Accordingly, experimental data (Mack and Rock 1998; O'Regan and Noë 2001; Chun and Marois 2002; Lavie 2006) and influential theoretical models (Posner 1994; Dehaene and Naccache 2001; Dehaene et al. 2006) have emphasized the links between spatial attention and perceptual consciousness. Strong evidence supporting this notion has also been provided by right brain-damaged patients affected by spatial neglect, whose acquired inability in orienting attention toward the contralesional left hemispace renders them unaware of left-sided stimuli (see Bartolomeo 2007, for a review).

In a recent event-related functional magnetic resonance imaging (fMRI) study (Chica, Paz-Alonso, et al. 2012), we used a visual paradigm based on laterally presented (left or right) near-threshold targets (i.e., consciously reported by the participants on only about 50% of the trials), preceded by spatially predictive peripheral cues presented at either valid or invalid locations (i.e., displayed at the same or at the opposite location as the subsequent target). We then explored hemodynamic signals across conditions to highlight some of the

brain regions that might demonstrate interactions between spatial attention and conscious perception (Chica, Paz-Alonso et al. 2012). A cortico-cortical network (including bilateral temporo-occipital regions, bilateral superior parietal lobes, the right angular gyrus, and the left intraparietal lobe) showed stronger activation for trials in which targets were reported as “seen” than for “unseen” targets, independently of cue validity. We thus hypothesized that this system could underlie a general pretarget onset preparatory state, independent of spatial orienting. Interestingly, a distinct, attentional orienting-dependent system, including the right intraparietal lobe and the left frontal eye field (FEF), was associated with the facilitatory effects of spatial orienting on conscious perception and, thus, depended on attentional orienting. In particular, the left FEF, a prefrontal node of the dorsal attentional network (Corbetta and Shulman 2002), emerged as a crucial area supporting the interaction between spatial attention and conscious perception; cues indicating the correct spatial location of the target induced an increased hemodynamic response in the left FEF for targets that would eventually be reported as seen than for targets which participants would deny having seen.

The implication of the left frontal lobe in attentionally mediated conscious perception is supported by several pieces of evidence. First, in intact humans, this notion is in agreement with fMRI and psychophysics evidence on the role of midline frontal sites (Haynes et al. 2005) and the left dorsolateral prefrontal cortex (Lau and Passingham 2006) conscious perception. Secondly, neurophysiological studies in nonhuman primates have also shown the implication of the FEF in discriminating a target from a set of distractors and signaling an impending eye movement response (Bichot and Schall 1999). Moreover, the late activation observed in FEF visual neurons might also interact with ongoing activity in visual cortical areas. By doing so, this area could contribute to the process by which a particular sensory representation receives enhanced activation and thereby engages attention and consciousness (Thompson and Schall 2000). These studies suggest that the FEF might be a key brain region in perceptual decision-making involved in conscious perception (Gold and Shadlen 2001). Thirdly, studies in human patients with right hemisphere damage and unawareness for left-sided events (visual neglect) suggest that a second focal lesion in the left frontal cortex (Vuilleumier et al. 1996), or a transcranial magnetic stimulation (TMS)-based inhibition of left prefrontal activity nearby the FEF region (Oliveri et al. 2001), has the ability to suppress such deficits.

Taken together, this evidence suggests that frontal cortical regions, anatomically remote from visual perceptual areas in the occipital regions of the brain, could be highly relevant for conscious perception (Vuilleumier et al. 2001). However, the correlational nature of the techniques used in some of these studies (including our own fMRI study) precludes determining whether such prefrontal contributions are rather epiphenomenal or a direct consequence of the crucial local processing leading to conscious access. Indeed, causality is a demanding concept that can only be attested by the behavioral effects of focal perturbations. Clinical observations do not always support the notion of frontal contribution to conscious perception, because patients with damage to the left prefrontal cortex do not usually appear to be perceptually unaware. However, it has recently been reported that these patients have an elevated masking threshold, which is in tight correlation with the degree of expansion of the lesion in the left anterior prefrontal cortex (Del Cul et al. 2009). Unfortunately, data from brain-damaged patients can be affected by attentional factors, such as reduced top-down attention or distractibility (Dehaene and Changeux 2011), and can be influenced by diaschetic effects and behavioral compensations. Evidence from brain-damaged patients can thus greatly benefit from other sources of data in order to reach firm conclusions about normal cognition.

In the present study, we used TMS in healthy participants to noninvasively interfere with time-specific neural events in the left FEF, an area that our previous fMRI study highlighted as a key region mediating the interactions between spatial attention and conscious perception (Chica, Paz-Alonso, et al. 2012). The left FEF was specifically selected for this study on the basis of its easy accessibility, its suggested implication in the modulation of conscious perception in right brain-damaged patients (Vuilleumier et al. 1996; Oliveri et al. 2001), and our ability to effectively impact it with TMS at a reasonable intensity level, as proven by prior experiments performed in its homotopic right hemisphere region, which aimed at modulating saccade planning and execution (Thickbroom et al. 1996; Ro et al. 2002; Olk et al. 2006), attentional orienting (Capotosto et al. 2009), as well as studying long-range connectivity leading to visual excitability modulations (Silvanto et al. 2005; Silvanto et al. 2006), and inducing visual perceptive ameliorations (Ruff et al. 2006; Chanes et al. 2012). The aim of the present study was to provide direct causal evidence about the potential implication of this area on the processes leading to consciousness and to explore whether the role of the left FEF in conscious perception was mediated or not by systems involved in attentional orienting. We thus delivered active or sham time-locked triplets of TMS pulses at key intervals for attentional processing induced by spatially predictive peripheral cues, and measured potential trial-by-trial interferences on 2 sequential tasks: An objective visual discrimination task (forced-choice discrimination of grating's lines orientation), known to be strongly modulated by attentional orienting in space (Chica, Lasaponara, et al. 2011), and a subjective detection task (based on a conscious detection of the target, indicating whether it was present or absent, and localization of its position if present), intended to assess access to consciousness for visual information. The TMS targeted the average group coordinates of our prior fMRI study (Chica, Paz-Alonso, et al. 2012), and was intended to provide direct causal evidence of its implications in such processes.

We predicted that if the left FEF played a causal role in conscious perception, then participants' conscious reports during attentional orienting should be significantly impacted in active as compared with sham TMS trials. Additionally, both the objective and subjective visual tasks were orthogonally manipulated (see also Chica, Lasaponara, et al. 2010; Chica, Botta, et al. 2012) to determine whether the potential contribution of the left FEF to consciousness was mediated or not by its known role on attentional orienting. Given the known role of the left FEF in spatial orienting to contralateral targets (Corbetta et al. 2008), its implications in the amelioration of awareness in neglect patients (Vuilleumier et al. 1996; Oliveri et al. 2001), as well as the increased hemodynamic response that we observed in the left FEF related to the interaction between spatial attention and consciousness (Chica, Paz-Alonso, et al. 2012), we specifically hypothesized that left FEF TMS would bias attentional orienting toward left (ipsilateral) targets. Biased orienting might in turn increase conscious perception of validly cued left (ipsilateral) targets, and/or impair the perception of invalidly cued right (contralateral) targets, that is, those presented in the unattended hemisphere, and preceded by invalid cues presented in the ipsilateral, and over-attended, hemisphere. Such results would supplement our own behavioral studies suggesting that spatial attention, triggered by peripheral cues, could be an important antecedent of conscious perception (Chica and Bartolomeo 2012), an evidence that is in line with theories proposing that spatial attention is a prerequisite for conscious perception (Posner 1994; Bartolomeo 2008).

Materials and Methods

Participants

Twelve participants (3 women, 1 left handed; mean age 24 years, standard deviation [SD]=4) gave their signed informed consent to participate in the study. Participants did not suffer any neurological or psychiatric condition and fulfilled all the necessary safety requirements to undergo MRI scanning and TMS procedures. They reported to have normal or corrected-to-normal vision and audition and were all naïve to TMS. The study was reviewed by the INSERM ethical committee and received the approval of an Institutional Review Board (CPP Ile de France 1, Paris, France). Participants first underwent a structural MRI scan, which was three-dimensional (3D) reconstructed and used to locate and follow in real time the TMS coil site. Participants were then carried over to the TMS session, which lasted for about 90 min.

Apparatus and Stimuli

E-prime software was used to control the presentation of stimuli, timing operations, and data collection (Schneider et al. 2002). Stimuli were presented against the gray background of an eye tracker screen (Tobii Technology AB, Danderyd, Sweden; 17" wide, 1024 × 768, 16-ms refresh rate; temporal and spatial resolution of 50 Hz and 0.25°, respectively). Three black boxes (6° high × 5.5° wide) were displayed, one in the center of the display, the other two placed 8.5° to the left or the right. The fixation point consisted of a black plus sign (0.5° × 0.5°) situated in the center of the central box. The cue was a square (6.7° high × 6.1° wide) presented around the left or the right box. The target was a grating with a spatial frequency of 3 cycles per degree of visual angle, and a diameter of 5.5°. It was tilted by 5° either to the left or to the right. There were 25 target stimuli, in which target contrast varied linearly between values of 0.02 and 0.09 Michelson contrast. Target contrast was manipulated before the experimental trials in order to adjust the percentage of consciously perceived targets to approximately 60%. This titration was done while

participants practiced the main task (see task description below). All participants started with a high contrast stimulus (Michelson contrast = 0.05), which was well above the threshold of conscious perception. Every 16 trials, target contrast was automatically adjusted using a “one-up-one-down” procedure until participants perceived approximately 60% of targets. If the percentage of correct detection rates was >65% of the trials, gratings at the immediately following lower contrast level were used for the next block; inversely, if the percentage of correct detection rates was <50% of the trials, gratings at the immediately following higher contrast level were used for the next block. The experimental trials started when participants felt comfortable with the task, and performance converged at a target contrast yielding approximately 60% of consciously perceived targets. This titration procedure continued during the whole experiment (every 14 trials during the experimental trials) to prevent factors such as practice or fatigue from influencing conscious perception.

Procedure

Figure 1A displays the sequence and timing of a trial. Trials started with a fixation point, lasting for 500 ms. The peripheral cue was then presented during 50 ms, and consisted of a square surrounding one of the peripheral markers, which was predictive about the spatial location of the incoming target on 67% of the target-present trials. Participants were informed that cues were predictive and encouraged to take cue spatial predictiveness into account in order to respond more accurately. However, they were not told the exact percentage of trials in which the cue predicted the target location. There was a single cue-to-target interstimulus interval (ISI) of 180 ms. During the

ISI, a burst made of 3 TMS pulses (either active or sham stimulation) was administered. The pulses were separated by 30 ms from each other. Active and sham pulses were delivered by 2 independent computer-controlled repetitive transcranial magnetic stimulation (rTMS) machines; they were randomly interleaved and embedded within the same block. On each trial, both active and sham TMS pulses started 50 ms after cue offset and ended 70 ms before target onset. The target was presented for 32 ms at either the left or the right marker, but never at the central location. No target was presented on 14% of the trials. Participants were required to provide 2 consecutive responses to the target. First, they were asked to discriminate the orientation of the grating lines with a forced-choice response (so-called objective task). They were required to press, with their right hand, on a computer keyboard, a left-sided key if the grating lines were oriented to the left, and a right-sided key if the grating lines were oriented to the right. Participants were encouraged to respond to every trial as fast and as accurately as possible within 2000 ms after target onset and requested to try to guess their response even when they did not see the stimulus. This visual grating discrimination task is referred to as “objective,” because it was planned as a forced-choice task. Participants could not opt out when unsure about having seen or not a target, and had to provide a response (left or right orientation) to every trial of the experiment. The objective task was used to control for the adequate deployment of attention in space according to the spatial information provided by the cue on each trial.

Secondly, we presented participants with 2 arrow-like stimuli (>>> or <<<), one below and the other above the fixation point. The vertical arrangement of the arrow-like stimuli ensured that participants could not prepare in advance a lateralized response prior to the

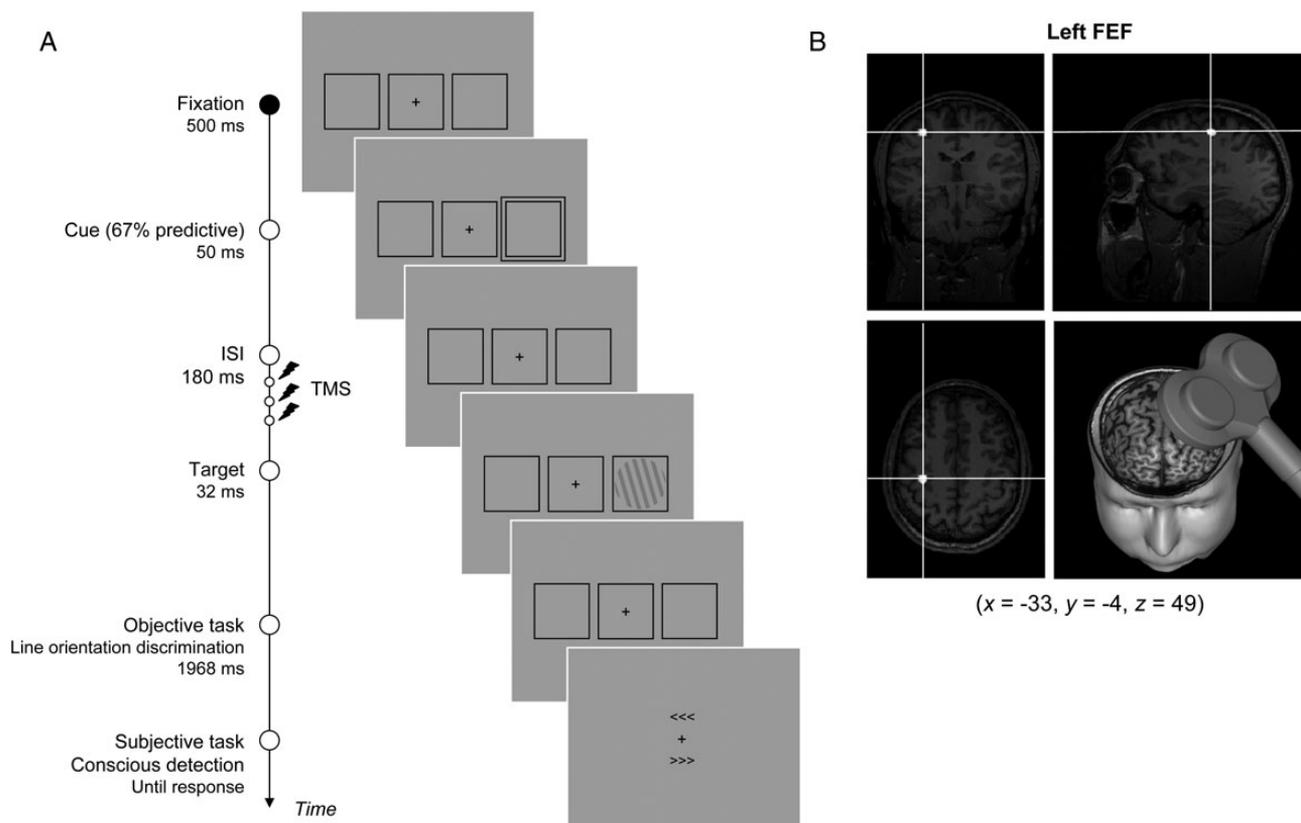


Figure 1. (A) Sequence of events in a given trial. A predictive peripheral cue preceded the target. It correctly predicted the location of the impending target on 67% of the trials. The target consisted of a “Gabor” patch, whose contrast was titrated, so that participants perceived approximately 60% of the target present trials. No target was presented on 14% of the trials. Participants performed 2 consecutive responses: An objective task (forced-choice discrimination of grating’s lines orientation), and a subjective task (based on their conscious detection of the target, indicating whether it was present or absent, as well as its position if present). (B) Coronal, axial, and sagittal MRI sections (top and bottom left, and top right, respectively) of a representative subject with the targeted left FEF location labeled as a white dot. The targeted left frontal site ($x = -33$, $y = -4$, $z = 49$) was extracted from the average MNI coordinates of a prior study (Chica, Paz-Alonso, et al. 2012). Such coordinates were labeled in each individual MRI and reconstructed 3D. By means of a frameless stereotaxic neuronavigation system, the TMS coil was placed and kept during the stimulation in the scalp location overlying the targeted brain region and oriented in a lateral to medial and rostral to caudal orientation (bottom right panel in the figure).

assigned response window on the basis of target location. We required participants to press, with their left hand, 1 of the 3 keys: An upper key (“d”), a lower key (“c”), or the space bar. The upper key always corresponded to the arrow presented in the upper part of the fixation point, while the lower key was associated with the arrow presented in the lower part of the fixation point. Participants were asked to report as accurately as possible, and in the absence of any time pressure, whether they had seen the target or not. If they had not, they were required to press the space bar. If they had seen the target, they were asked to indicate its location on the screen (left or right). This procedure allowed us to determine whether participants correctly localized targets reported as seen, and whether false alarms were reported at the same location as the previously cued (valid) location, or at the opposite (invalid) location. This task was referred to as “subjective,” because target contrast was adjusted, so that only 60% of the targets were perceived throughout the experimental blocks and, therefore, there was no correct response, as participants were required to indicate in each trial, whether they saw the target or not. The subjective task served to evaluate the ability of participants to consciously perceive the stimuli and, thus, to ascertain whether or not visual information had accessed consciousness. Note that the present use of the terms *objective and subjective* is the result of a convention in the literature on consciousness. (see, e.g., Dehaene and Changeux 2011). We employed these terms here for consistency with our previous fMRI study (Chica, Paz-Alonso, et al. 2012). As such, the theoretical value of these terms should not be overestimated. In particular, the present subjective responses were indeed based on participants’ subjective perception of the target, but they were of course objectively evaluated as being correct or incorrect.

To avoid TMS cumulative effects across trials, the duration of the arrow-like stimuli display was adjusted on a trial-by-trial basis, so that the duration of the whole trial was never shorter than 5 s. The experiment consisted of a total of 560 trials, 80 of which were target-absent trials.

TMS Targeting, Neuronavigation, and Pulse Delivery

Structural T_1 -weighted MRI scans were acquired for all participants at the CENIR MRI center (Salpêtrière Hospital in Paris). We used a 3-T Siemens magnetization prepared rapid gradient echo, flip angle 9° , repetition time = 2300 ms, echo time = 4.18 ms, slice thickness = 1 mm. Left FEF coordinates ($x = -33$, $y = -4$, $z = 49$, Fig. 1B) were taken from our previous fMRI study, in which we used the same behavioral paradigm to study the neural basis of the interactions between spatial attention and conscious perception (Chica, Paz-Alonso, et al. 2012).

SPM5 software (UCL, London, UK) running under Matlab 7.4 license (Mathworks, USA) was used to localize and to mark the left FEF region in each individual brain. We first created the region of interest in the MNI space using the Marbars toolbox for Matlab (<http://marsbar.sourceforge.net/>). The region of interest was defined by a sphere, 5 mm in diameter, centered in the above mention coordinates of the left FEF ($x = -33$, $y = -4$, $z = 49$). The structural images of the participants were segmented into white and gray matter. The left FEF region was then denormalized using the inverse segmentation matrix created for each participant (spatial smooth isotropic Gaussian Kernel of 1-mm full-width half-maximum). The resulting region was coregistered with the participant’s structural image, which resulted in the precise location of this area for each individual brain.

In our prior fMRI study, the left FEF ROI was identified in the contrast cue > jitter fixation (false discovery rate corrected, $q > 0.001$). The center of mass of this left FEF ROI (i.e., $-33 -4 49$) exactly corresponded to the highest local maxima found within this left FEF cluster (z -score = 5.20). This cluster contained a total of 77 voxels with the following maximum/minimum (mm): $X = -39/-23$; $Y = -9/0$; and $Z = 42/55$. Based on this ROI, we selected the targeted TMS left FEF region in the current study as a 5-mm sphere centered in the same highest local maxima and center of mass as the ROI used in the prior fMRI study. This ROI sphere contained a total of 56 voxels that fell within the cluster identified in the prior fMRI study (maximum/minimum (mm) in $X = -36/-30$; $Y = -8/0$; and $Z = 46/52$). It should be noted that in our prior fMRI study data from participants who had

a head motion over 2.5 mm during imaging (where 2.5 mm corresponds to the in-plane voxel dimensions) were excluded from the analysis. Moreover, to correct for motion artifacts of < 2.5 mm, we used the standard SPM preprocessing routines and the motion adjustment and artifact repair tools provided by the ArtRepair Software (Stanford Psychiatry Neuroimaging Laboratory). Thus, the exact correspondence between the targeted TMS left FEF and the left FEF ROI, showing an interaction between spatial attention and conscious perception in our prior fMRI study, was carefully controlled.

Aside from this, given the spatial resolution of online TMS patterns with an impact that can spread across an area of 12–15 mm radius around the TMS coil center, effective interference of the targeted area can be achieved in spite of small interindividual or group differences in fMRI loci or coil location.

TMS Procedure and Navigation

Three TMS pulses were delivered during the cue-to-target ISI. The first pulse started 50 ms after cue offset. Pulses were separated by 30 ms and finished 70 ms before target onset. We used 2 biphasic repetitive TMS devices (Superapid2, Magstim, Withland, UK), and a set of 70 mm TMS figure of 8 coils held tangentially to the skull with the axis of the coil angled approximately 45° in a rostral-to-caudal and lateral-to-medial orientation (i.e., parallel to the precentral sulcus). The TMS coil was positioned on the area of interest by means of a 2-mm precision neuronavigation system (eXimia NBS System, Nexstim, Helsinki, Finland), capable of estimating and tracking in real time the relative position of our figure of 8 coil on the sectional and 3D reconstruction of the participants’ MRI.

The left FEF was localized in the 3D MRI reconstruction and labeled, so that the coil and the perpendicular projection of the estimated magnetic field accurately coincided with the center of such area. All participants received stimulation at suprathreshold levels with respect to their individual motor thresholds. We initially aimed to use a TMS intensity around 65% maximum stimulator output throughout all the participants, a level of stimulation around intensity levels ($\pm 10\%$ variability) that have demonstrated in prior similar studies an effective impact of the FEF region (Ruff et al. 2006; Silvanto et al. 2005, 2006; Chanes et al. 2012). Nevertheless, as done elsewhere (Chica, Bartolomeo, et al. 2011; Chanes et al. 2012), stimulation was adapted in those individuals in which TMS induced facial or tongue sensations, involuntary blinks, jaw activations, or motor activations in the contralateral hand, until those events were no longer induced. The final mean stimulation intensity was 55% ($SD = 6$), a level that corresponded on average to 89% ($SD = 6$) of each individual motor threshold. A second coil was placed near the actively stimulated site, with its edge as close as possible to that location, and positioned at 90° with its surface pointing away from the skull. In our group of TMS naïve participants, and as demonstrated previously (Chanes et al. 2012), this procedure was effective in mimicking the clicking noise associated with the delivery of TMS pulses, while effectively preventing the magnetic field from significantly reaching and stimulating the brain. This sham procedure allows to optimally deliver left lateralized sham TMS pulses in a randomized manner, on a very similar scalp area. Sham pulses could be anticipated by participants, because they were embedded within the same experimental block as active pulses. Given the technical limitations of commercially available coils, scalp tapping sensation could only be incompletely mimicked in our experiment. Nevertheless, all our participants were naïve about TMS and due to the high difficulty of the behavioral paradigm, they had to be deeply focused on performing the visual task. Hence, any anticipation or discrimination of online sham or active bursts, which were randomly interleaved, was highly unlikely.

Results

Results from the objective task (discrimination of grating line orientation) were used to determine whether participants did attend, as expected, to the location indicated by the

visuo-spatial cue. Response times (RTs) faster than 150 ms, were eliminated from the analyses as outliers (1.05% of the trials for sham TMS, and 0.49% of trials for active TMS). In the objective task, participants were instructed to optimize both accuracy and RTs. It is well known that, under these conditions, speed-accuracy trade-off-based strategies are commonly adopted, and that participants can respond faster but less accurately to attended targets (Roder et al. 2007; Chica, Taylor, et al. 2010; Chica, Bartolomeo, et al. 2011). We thus used an index of behavioral effects, known as “inverse efficiency” (IE, mean RT/proportion correct; Townsend and Ashby 1983). IE is artifact free of speed-accuracy trade-offs and combines RT and accuracy in a single variable, which has been successfully used in some of our prior experiments (Chica, Bartolomeo, et al. 2011). Detailed inspection of mean RTs and accuracy data for each experimental condition, presented in Table 1, shows some speed-accuracy trade-offs in the objective discrimination task; for example, RTs were faster but less accurate for valid than for invalid targets presented ipsilaterally in sham TMS trials. We therefore considered IE as a better measure to understand the outcomes in the objective discrimination task (see mean RT and accuracy data used for calculations in Table 1, and significant main effects and interactions for these 2 parameters in Table 2).

Responses to the subjective task indicated participants’ conscious perception and its modulation by spatial attention and TMS bursts. We also calculated d' and beta values, parameters used in signal detection theory (SDT), as outcome measures for the subjective task (Table 1). The d' parameter is a bias-free statistic that provides a measure of observers’ ability to detect signals, while beta describes their relative preference for one response over the other. To compute those 2 parameters, trials in which the location of a target presented in the screen was correctly determined by participants were considered as correct detections, or “hits”; trials in which the presence of a present target was not acknowledged by participants were considered as “misses”; trials in which participants reported the location for targets that were not presented on the screen were treated as “false alarms”; trials in which the target was absent and participants correctly reported not to have seen it were considered “correct rejections”; finally, trials in which the location of a present target was incorrectly reported by participants in the subjective task were excluded from the analyses as errors, that is, trials in which participants reported to have seen a target, but incorrectly localized its screen location as within the left or the right marker (2.67%

of seen targets in the sham TMS trials and 3.16% in the active TMS trials).

Trials in which participants failed to maintain gaze at fixation (1.79% of the trials in the sham TMS and 2.63% in the active TMS) were excluded from further analyses. Three participants had to be excluded from the analyses because one of their mean response parameters deviated more than 3 SD from the group mean; an error rate on the subjective task larger than 20%, a percentage of false alarms on the subjective task larger than 40%, and a rate of eye movements larger than 10% in at least one of the conditions, respectively.

Objective Task (Grating Line Orientation Discrimination)

We performed a repeated-measures analysis of variance (ANOVA) on seen targets with the factors of Target Location (ipsilateral vs. contralateral with regards to the TMS stimulated site, the left FEF), Validity (valid vs. invalid trials), and TMS (active vs. sham). A significant interaction between Target Location and TMS was observed, $F_{1,8} = 5.68$, mean squared error (MSE) = 2146, $P = 0.044$. This is in agreement with previous TMS studies (see, e.g., Pascual-Leone et al. 1994; Hilgetag et al. 2001; Thut et al. 2005), which found different TMS effects for ipsilateral and contralateral targets. Given the significant interaction between Target Location and TMS, we performed separate ANOVAs for ipsilateral and contralateral targets.

For ipsilateral targets, there was a main effect of TMS, $F_{1,8} = 15.74$, MSE = 843, $P = 0.004$, and a significant interaction between Validity and TMS, $F_{1,8} = 11.39$, MSE = 483, $P = 0.010$. This interaction was explained by an increased cue validity effect when active versus sham TMS was applied to the left FEF (Fig. 2). For contralateral targets, only the main effect of Validity was significant, $F_{1,8} = 6.55$, MSE = 4058, $P = 0.034$. These results indicate that TMS over the left FEF biased attentional orienting to the left visual hemisphere, ipsilateral towards the stimulated region.

Subjective Task (Conscious Detection)

SDT parameters, d' and beta, were analyzed by using 2 separate ANOVAs, with the factors of Target Location (ipsilateral vs. contralateral to the left stimulation site), Validity (valid vs. invalid trials), and TMS (active vs. sham). For the perceptual sensitivity index (d'), there was a significant interaction between Target Location and TMS, $F_{1,8} = 6.09$, MSE = 0.161, $P = 0.039$. Pair-wise t -tests demonstrated that TMS significantly

Table 1

Objective task. Mean RT, accuracy, IE, and validity effect for the IE scores

	Ipsilateral (left targets)				Contralateral (right targets)			
	Sham TMS		Active TMS		Sham TMS		Active TMS	
	Valid	Invalid	Valid	Invalid	Valid	Invalid	Valid	Invalid
RT	668	758	695	791	678	730	692	740
ACC	0.95	0.98	0.95	0.94	0.95	0.94	0.97	0.98
IE	706	776	734	838	717	777	714	762
Validity effect (IE)	70		104		60		48	
d'	1.99	1.92	2.35	2.11	2.25	2.17	2.31	1.73
Beta	8	13	9	12	13	16	10	6

Note: Subjective task: mean d' and beta scores. Each score is shown for each condition of Target Location (ipsilateral vs. contralateral to the stimulation site), TMS (active vs. sham TMS), and Validity (valid vs. invalid trials).

Table 2

Objective task

RT results		Accuracy results	
Validity	$F_{1,8} = 6.46$, $P = 0.035$	Target Location × TMS	$F_{1,8} = 6.42$, $P = 0.035$
TMS	$F_{1,8} = 12.74$, $P = 0.007$	Validity × TMS	$F_{1,8} = 5.95$, $P = 0.041$
All other P s	> 0.312	Target Location × Validity × TMS	$F_{1,8} = 3.50$, $P = 0.098$
		All other P s	> 0.298

Note: Results of the mean RT and accuracy repeated-measures ANOVA on seen targets with the factors of Target Location (ipsilateral vs. contralateral with regards to the TMS stimulated site, the left FEF), Validity (valid vs. invalid trials), and TMS (active vs. sham). Significant main effects and interactions are reported. The close to significance interaction between Target Location, Validity, and TMS in the accuracy analysis is also shown.

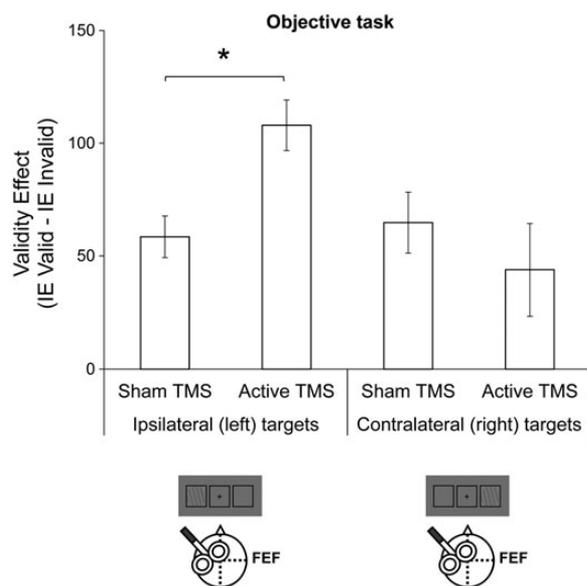


Figure 2. Effects of left FEF stimulation in the objective task. Validity effect (mean RT for invalid minus valid trials), for the IE scores, as a function of TMS (sham and active), and target location (ipsilateral and contralateral to the stimulated region). Higher scores indicate larger validity effects. Asterisks represent statistically significant differences between conditions. Error bars represent standard error of the mean. Active left FEF TMS increased the validity effect when compared with sham stimulation for targets presented ipsilaterally to the stimulated (left) site, whereas no significant differences were found for right, contralateral targets.

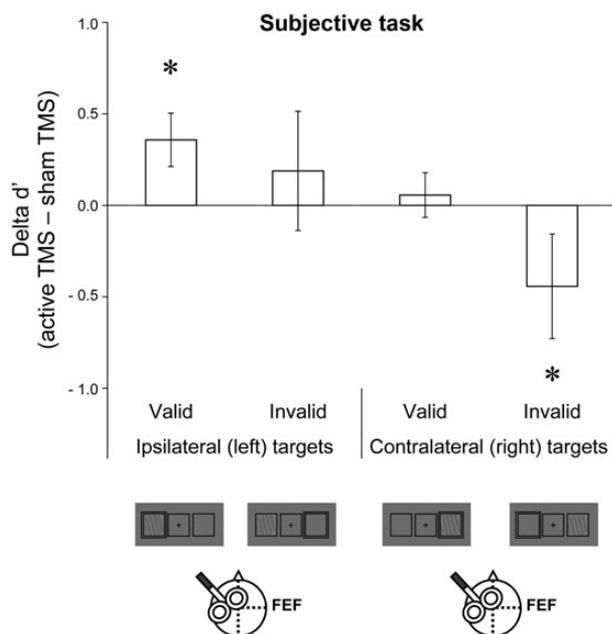


Figure 3. Effects of left FEF stimulation in the subjective task. Delta d' (active minus sham TMS trials), as a function of target location (ipsilateral and contralateral to the stimulated region), and validity (valid and invalid trials). Scores above 0 indicate larger d' for active versus sham TMS trials; scores under 0 indicate impaired d' for active versus sham trials. Asterisks represent values significantly different from 0. Error bars represent standard errors of the mean. TMS improved perceptual sensitivity for ipsilateral (left-sided) validly cued targets and impaired perceptual sensitivity for contralateral (right-sided) invalidly cued targets.

improved perceptual sensitivity for ipsilateral (left visual hemifield) valid targets when active versus sham TMS was applied, $P=0.024$ (Fig. 3). In contrast, TMS significantly

impaired perceptual sensitivity for contralateral invalidly cued targets, $P=0.001$. Separate ANOVAs for ipsilateral and contralateral targets revealed a pattern toward increased d' for ipsilateral targets on active versus sham TMS trials, although no significant main effects or interactions were observed ($P>0.155$ for all comparisons). Importantly, a significant interaction between Validity and TMS was observed for contralateral targets, $F_{1,8}=6.10$, $MSE=0.092$, $P=0.039$. This interaction revealed that left FEF TMS reduced perceptual sensitivity (d') for invalid trials as compared with valid trials (Table 1).

The analysis of mean response bias (beta) values demonstrated a marginally significant main effect of TMS, $F_{1,8}=5.10$, $MSE=49.50$, $P=0.054$, and a marginally significant interaction between Target Location and TMS, $F_{1,8}=3.92$, $MSE=18.86$, $P=0.083$. Separate ANOVAs for ipsilateral and contralateral targets demonstrated that, for ipsilateral targets, only the main effect of Validity was significant, $F_{1,8}=6.04$, $MSE=21.53$, $P=0.039$; response criterion was more relaxed for valid than for invalid trials, as previously observed with a similar behavioral paradigm (Chica, Lasaponara, et al. 2011). For contralateral targets, a main effect of TMS, $F_{1,8}=10.98$, $MSE=41.40$, $P=0.011$, and a significant interaction between Validity and TMS, $F_{1,8}=6.45$, $MSE=17.90$, $P=0.035$, were observed. The Validity \times TMS interaction revealed that the response criterion was more relaxed (less conservative) under active than under sham TMS for invalid trials (Table 1).

To summarize, results from the objective task (grating line orientation discrimination) demonstrated that TMS delivered to the left FEF biased attentional orienting to the left (ipsilateral) visual hemisphere. This biased attentional orienting was accompanied by increased perceptual sensitivity to consciously perceive ipsilateral (left) targets preceded by ipsilateral (valid) cues. Complementarily, perceptual sensitivity (d') was decreased for ipsilateral invalid cues in the subjective task for targets presented in the contralateral (right) hemisphere. This effect was also accompanied by a more relaxed response criterion. Altogether, our results suggest that: 1) spatial orienting and conscious perception interact in complex ways, through frontal regions such as the left FEF; 2) the left FEF, which is remote from the visual cortex, plays a causal role in conscious perception, and this influence is mediated by spatial attention.

Discussion

Prior research has solidly demonstrated the important role of the FEF as part of a bilateral dorsal visuo-spatial system for the orienting of spatial attention (Corbetta et al. 2008). In contrast, the details of frontal contributions to conscious perception previously suggested elsewhere (Grosbras and Paus 2002, 2003; O'Shea and Walsh 2004; Smith et al. 2005) invited further exploration. At variance with previous studies, we compared the interfering effects of active TMS pulses by means of a totally embedded and interleaved lateralized sham TMS condition delivered in a random order throughout the same experimental block. Furthermore, we selected a specific left frontal site within the boundaries of the left FEF, on the basis of prior fMRI evidence based on a similar behavioral paradigm (Chica, Paz-Alonso, et al. 2012). This correlational evidence pointed out at this left frontal location as one of the key brain regions that mediate the interactions between

spatial attention and conscious perception. The present findings rule out the possibility that such fMRI-based relation was epiphenomenal in nature, and confirm, through a TMS perturbation experiment, the causal contribution of the left FEF in providing access to consciousness for visual stimuli.

The present results expand prior evidence in demonstrating the particular contribution of the left FEF to facilitate access to conscious processing of visual stimuli. Perceptual sensitivity was enhanced for ipsilateral targets preceded by valid cues presented on the same side of space. Additionally, invalid (ipsilateral) cues decreased perceptual sensitivity for contralateral targets. Furthermore, the analysis of the objective task (grating's line orientation discrimination) strongly suggests that such effects might not operate directly on conscious access, but are likely to be mediated through the role of the stimulated area on spatial attentional orienting. Specifically, active left FEF stimulation appeared to increase the effects of cue validity ipsilaterally. Alternatively, however, FEF TMS could also have modulated perceptual rather than attentional processes, by influencing cue saliency. The nature of our spatial cue (a salient object presented in the periphery) could make this explanation plausible. Note, however, that perceptual and attentional accounts are not exclusive. For example, some authors consider spatial attention, triggered by peripheral cues, as a perceptual process that computes perceptual saliency to orient attention and eye movements to a selected location (see, e.g., Godijn and Theeuwes 2002; Lupiáñez 2010).

Three issues of our results are particularly worth discussing. First, in our experiment, left FEF TMS (intended at interfering with the processing of the spatial cue) did not reduce, but instead increased cue validity effects in the discrimination of ipsilateral (left) targets. Such patterns of facilitatory effects after local perturbations are in strong agreement with the results of prior unilateral rTMS experiments in the right posterior parietal cortex (Pascual-Leone et al. 1996; Hilgetag et al. 2001; Thut et al. 2005) or frontal regions (Grosbras and Paus 2002; Chanes et al. 2012). Mechanisms based on interhemispheric rivalry (Sprague 1966; Kinsbourne 1977; Hilgetag et al. 1999; Payne and Rushmore 2004; Valero-Cabre et al. 2006) have been frequently invoked to explain such paradoxical improvements after posterior parietal stimulation. Applied to our TMS experimental manipulation, left FEF interference might have imbalanced a finely regulated balance of excitability between left and right fronto-parietal networks, thus biasing attentional orienting effects ipsilaterally and influencing participants' ability to efficiently process visual information during the objective and subjective tasks. This explanation is consistent with the recent fMRI data indicating that although in visual attentional tasks activations in the right hemisphere tend to be larger than in the left hemisphere, the left FEF and left intraparietal sulcus (IPS) generate stronger contralateral attention signals than their right-hemisphere counterparts. The left FEF and left IPS may thus counteract the right hemispheric asymmetry and balance the fronto-parietal system for spatial attentional control (Szczepanski et al. 2010).

Secondly, our results demonstrate that the left FEF modulates conscious perception for ipsilateral targets preceded by valid (left) cues and contralateral targets preceded by invalid (left) cues. Prior human rTMS studies have demonstrated significant patterns of neglect-like effects for contralateral targets

following right frontal or parietal stimulation (Pascual-Leone et al. 1994; Hilgetag et al. 2001; Grosbras and Paus 2002; Thut et al. 2005). Nevertheless, our result has little precedence in the TMS or rTMS human literature, where perturbation of left frontal or parietal systems usually caused more moderate modulatory effects on unilateral contralesional targets, with outcomes that ranged from nonsignificant detection degradations (Hilgetag et al. 2001), to cue validity dependent decreases in detection reaction times (Grosbras and Paus 2002), moderate increases in visual sensitivity measures (Grosbras and Paus 2003), or even cancellations of the cost generated by invalid cues (Smith et al. 2005).

Finally, the punctual interference of the left FEF during the cue driven orienting period also modulated conscious visual reports. Biased attention to the ipsilateral (left) hemispace increased conscious perception of validly cued ipsilateral targets and impaired that of invalidly cued contralateral (right-sided) targets. Very importantly, this effect occurred not only in terms of response criterion or subjective reportability levels, but also as shifts in perceptual sensitivity (d'). This result is crucial to our predictions, because it shows that stimulation of a frontal region, remote from visual areas, can have an effect on conscious access, by modulating not only the reportability threshold, but also perceptual sensitivity.

To the best of our knowledge, this is the first TMS study that has specifically targeted the left FEF with the aim of providing causal evidence of the role of this area in attentionally modulated access to visual consciousness. As already mentioned, the current study was planned as a follow-up project aimed at ruling out whether the left FEF activation we found in a previous fMRI study (Chica, Paz-Alonso, et al. 2012) was simply epiphenomenal or it was supported by a genuine causal contribution of the left FEF to conscious visual perception. The TMS manipulation of the FEF mainly in the right hemisphere has been used for many years to probe its role in saccadic planning and execution (Thickbroom et al. 1996; Ro et al. 2002; Olk et al. 2006), cue processing, and spatial attentional orienting (Smith et al. 2005; Capotosto et al. 2009), visual perception and visual consciousness modulations (Grosbras and Paus 2002, 2003; Smith et al. 2005; Ruff et al. 2006; Chanes et al. 2012), and to study long-range connectivity leading to visual excitability (Silvanto et al. 2005, 2006). Similar studies targeted other regions and showed that the manipulation of the right or left IPS, or the right MT/V5 regions, can also induce modulations in preattentive or top-down attentional orienting processes, which resulted in visual detection performance enhancements (Pascual-Leone et al. 1996; Hilgetag et al. 2001; Thut et al. 2005). Interestingly, in the absence of any specific network-based hypotheses, as the ones provided by our fMRI study (Chica, Paz-Alonso, et al. 2012), the causal contributions of the left frontal systems to attentional orienting, visual processing, and conscious perception remained to date poorly explored. In a few studies, left frontal regions have been causally examined in spatially cued visual tasks, mainly as a comparison with the effects of its right counterpart (Grosbras and Paus 2002, 2003; Smith et al. 2005). In these studies, left frontal TMS determined weak effects exclusively for contralateral (right-sided) targets, which were in contrast with the strong and highly significant bilateral contributions of the right FEF. Nevertheless, none of these studies titrated stimulus saliency and manipulated attentional orienting and conscious perception

orthogonally as we did in the present study. Also of importance, none of these prior studies selected their frontal targets on the basis of a prior fMRI study using a similar paradigm. They used instead pre-established anatomical coordinates, sometimes confirmed with TMS-based saccade planning localizers. Overall, the main conclusion of all these prior studies is that the left FEF may weakly contribute to the modulation of conscious detection of targets presented in the contralateral right visual hemifield, when compared with its right FEF counterpart, which shows strong bilateral effects. Interestingly, however, such weak case for a primary role of the left FEF in conscious perception is in contrast with evidence from focally damaged patients. This evidence shows that the lack of awareness to left visual targets after a right hemisphere lesion can be counteracted by a subsequent lesion (Vuilleumier et al. 1996) or suppressive TMS on left frontal areas (Oliveri et al. 2001), which strongly hints at the crucial role of this area in such processes.

The left FEF is a part of the dorsal fronto-parietal network involved in attentional orienting (Corbetta and Shulman 2002; Corbetta et al. 2008). In our fMRI study (Chica, Paz-Alonso, et al. 2012), an efficient coupling of this network during attentional orienting was related to seen reports with valid cues (and therefore spatial attention was located at the target location), but it was associated with unseen reports when cues were invalid (and therefore spatial attention was located at the wrong location; see also Chica, Lasaponara, et al. 2010; Chica, Botta, et al. 2012). In agreement with some past and recent causal evidence indicating the ability of right FEF TMS to enhance visual conscious detection (Grosbas and Paus 2002; Chanes et al. 2012), these findings suggest that the left FEF region is part of a broader attentional network supporting the interaction between spatial attention and conscious perception, which is likely to involve frontal and parietal sites in both hemispheres. Future experiments will need to address and detail the likely contribution of those other cortical regions in conscious perception and their structure as a network.

In conclusion, our results demonstrate in healthy participants that an imbalance of the dorsal fronto-parietal attentional network, resulting from TMS interference on the left FEF during the orienting period, biases attentional orienting and modulates conscious reports. The current level of detail in the knowledge of the functioning of the fronto-parietal attentional networks does not allow us to precisely relate the present results to a complete theoretical framework. Nevertheless, our findings are in line with models postulating a tight relationship between spatial attention and conscious perception (Posner 1994; Dehaene and Naccache 2001; Dehaene et al. 2006; Bartolomeo 2008) and clarify some of the brain mechanisms underlying their interactions. The finding that the interference on a frontal node of attentional networks (and probably on its connections with parietal regions; Chica, Paz-Alonso, et al. 2012) can bias attentional orienting and conscious perception is in line with evidence supporting the important role of fronto-parietal interactions in attentional orienting and visual consciousness (Beck et al. 2001; Dehaene and Naccache 2001; Thiebaut de Schotten et al. 2005; Dehaene et al. 2006; Chica and Bartolomeo 2012; Chica, Paz-Alonso, et al. 2012). Thus, the present evidence represents a step in specifying the contributions of the cortical nodes of the fronto-parietal attentional networks to conscious visual perception.

Notes

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