

Brief Communications

Causal Frequency-Specific Contributions of Frontal Spatiotemporal Patterns Induced by Non-Invasive Neurostimulation to Human Visual Performance

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Neural oscillatory activity is known to play a crucial role in brain function. In the particular domain of visual perception, specific frequency bands in different brain regions and networks, from sensory areas to large-scale frontoparietal systems, have been associated with distinct aspects of visual behavior. Nonetheless, their contributions to human visual cognition remain to be causally demonstrated. We hereby used non-uniform (and thus non-frequency-specific) and uniform (frequency-specific) high-beta and gamma patterns of noninvasive neurostimulation over the right frontal eye field (FEF) to isolate the behavioral effects of oscillation frequency and provide causal evidence that distinct visual behavioral outcomes could be modulated by frequency-specific activity emerging from a single cortical region. In a visual detection task using near-threshold targets, high-beta frequency enhanced perceptual sensitivity (d') without changing response criterion (beta), whereas gamma frequency shifted response criterion but showed no effects on perceptual sensitivity. The lack of behavioral modulations by non-frequency-specific patterns demonstrates that these behavioral effects were specifically driven by burst frequency. We hypothesize that such frequency-coded behavioral impact of oscillatory activity may reflect a general brain mechanism to multiplex functions within the same neural substrate. Furthermore, pathological conditions involving impaired cerebral oscillations could potentially benefit in the near future from the use of neurostimulation to restore the characteristic oscillatory patterns of healthy systems.

Introduction

Evidence in support of the fundamental role played by cerebral oscillations in cognitive processing has strongly emerged in the last decades. In the particular domain of visual perception, prior work has indicated that for different brain regions and systems, from sensory areas to large-scale frontoparietal networks exerting top-down influences on visual processing and behavioral performance, oscillatory activity at specific frequency bands might contribute to distinct aspects of behavior (Donner et al., 2007;

Fries, 2009; Siegel et al., 2011). However, the specific role of neural oscillatory frequency remains to be causally isolated.

For nearly two decades, the ability of non-invasive neurostimulation to depolarize local neuronal clusters and interfere with neural processing has been used to establish, in several cognitive domains, causal associations between brain regions and behaviors (Wagner et al., 2007). Recently, by comparing the behavioral modulations obtained at different frequencies, transcranial alternate current stimulation and short-burst and repetitive transcranial magnetic stimulation (TMS) have been used in the investigation of the oscillatory basis of human cognition (Klimesch et al., 2003; Kanai et al., 2008; Romei et al., 2010, 2011; Feurra et al., 2011). More importantly, seminal work performed in this field has demonstrated that uniform TMS bursts can entrain rhythmic brain oscillation patterns tuned to the applied input frequency (Thut et al., 2011).

In the present study, we compared the behavioral impact of frequency-specific (or uniform) and non-frequency-specific (or non-uniform) TMS patterns delivered over a right frontal region to provide causal evidence in humans on the modulatory role of high-beta and gamma activity to distinct aspects of human visual performance. For both frequencies, these two types of TMS patterns had equal duration and number of pulses. Nonetheless, in frequency-specific patterns pulses were uniformly distributed across the duration of the burst, whereas in non-frequency-

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specific patterns, those were delivered at fixed unequal interpulse intervals. This approach warrants the delivery of an identical amount of activity during the same time interval in both types of bursts, isolating the specific impact of stimulation frequency to behavior.

We targeted the right frontal eye field (FEF), a site involved in visuospatial attentional orienting (Corbetta and Shulman, 2002; Corbetta et al., 2008) and conscious perception (Grosbras and Paus, 2003; Moore and Armstrong, 2003; Libedinsky and Livingstone, 2011; Chanes et al., 2012), holding rich interactions with parietal and occipital brain regions, that can engage in high-beta (30 Hz) and gamma (50 Hz) oscillatory activity (Fries et al., 2001; Buschman and Miller, 2007; Gregoriou et al., 2009). More specifically, Buschman and Miller (2007) reported a differential involvement of these two oscillation frequencies in a pop-out and a visual search task engaging, respectively, exogenous and endogenous attentional orienting processes, which are known to induce distinct behavioral influences on human visual performance (Chica et al., 2011). We hypothesized that uniform TMS bursts delivered over the right FEF at high-beta versus gamma frequency would yield frequency-specific effects on visual performance, compared with their equivalent non-uniform TMS patterns not tuned to any particular frequency.

Materials and Methods

Two groups of 14 participants (6 women and 8 men and 10 women and 4 men), aged between 19 and 39 years (average of 25 ± 3 and 25 ± 6 years old) reporting no history of neurological or psychiatric disorders and normal or corrected-to-normal vision, took part in the experiments. Twenty-three of them were naive as to TMS and to the purpose of the experiments, and they all participated voluntarily. The protocol was reviewed by the Inserm ethical committee and approved by an Institutional Review Board (CPP Ile de France 1).

Apparatus, stimuli, and procedure. Visual stimuli were displayed on an eye-tracker screen (Tobii Technology AB; 17 inches wide, 1024×768) using a laptop computer (Dell Latitude E6400) and standard stimulus presentation software (E-Prime Software). Each trial started with a gray resting screen (luminance: 75 cd/m^2 , 2500 ms), followed by a fixation screen (randomly lasting between 1000 and 1500 ms) (Fig. 1a). The fixation cross ($0.5 \times 0.5^\circ$) was displayed in the center, along with three rectangular boxes ($6.0 \times 5.5^\circ$): one central and two lateral ones (centered 8.5° to the left and right of the fixation point). Then, the fixation cross became slightly larger ($0.7 \times 0.7^\circ$, 66 ms) to alert participants of an upcoming event. After an interstimulus interval (233 ms), a target appeared at the center of one of the two lateral boxes for a brief period of time (33 ms). The target consisted of a low-contrast Gabor stimulus (2 cycles/degree spatial frequency, 3.0° diameter, 0.3° of SD, minimum and maximum Michelson contrast of 0.031 and 0.283, respectively) with its lines tilted 1° to 10° clockwise or counterclockwise. The intertrial interval lasted at least 4 s.

Participants were asked to execute two tasks. The first task was to determine the orientation of the Gabor lines (discrimination task) by pressing the corresponding button on a computer keyboard (“1” for left and “2” for right) with the index and middle fingers of their right hand. Participants were forced to guess a response even when the target was not present or they did not consciously perceive it and accuracy was collected as outcome measure. The second task was to report whether they had consciously perceived the Gabor or not (conscious detection task). To do so, two arrow-like stimuli ($<<<<$ and $>>>>$) pointing to the left and to the right were simultaneously presented below and above the fixation cross. Participants were provided with 3 keys, which they had to operate with their left hand: an upper key “d,” a lower key “c,” and the space bar. The upper and lower keys were associated to the arrows presented on the top and the bottom, respectively. Participants had to respond by pressing the space bar if they did not see the stimulus, or the key (“d” or “c”) to select the arrow pointing to the visual hemifield (right/left) in which they

perceived the target. The location of each arrow, above or below the fixation point, was randomized across trials. This task was assessed through perceptual sensitivity (d') and response criterion (beta), two measures used in Signal Detection Theory (Green and Swets, 1966; Macmillan and Creelman, 2005). Perceptual sensitivity is a bias-free measure that informs on participants' ability to detect weak signals in situations that might be strongly influenced by belief. Response bias (beta) describes the relative preference of participants for one response over the alternative one, independently on signal strength. When participants favor neither a “yes, I saw it” response nor a “no, I did not see it” response, beta is equal to 1. Values lower than 1 indicate a bias toward the affirmative response, whereas values >1 indicate a bias toward the negative response. To compute these measures, trials in which the location of a target was correctly determined by participants were considered as correct detections or “hits”; trials in which the presence of the target was not acknowledged were counted as “misses”; trials in which participants reported the location for targets that were not presented were considered “false alarms”; trials in which the target was absent and participants correctly reported not to have seen it were considered “correct rejections”; and, finally, trials in which the location of a present target was incorrectly reported were counted as “errors” and excluded from further analyses. Eye movements were monitored during each trial for fixation control purposes. Fixation was considered broken when participants' eyes position was recorded outside the central box (i.e., 3° away from the fixation cross horizontally and 2.75° vertically).

A titration procedure performed before the onset of the experiment allowed us to determine for each participant the stimulus contrast at which $\sim 50\%$ of the displayed targets were consciously reported. The degree of line tilting was also adjusted to maintain discrimination accuracy between 65 and 85% of correctly reported targets. Such titration levels ensured that in both tasks, performance was halfway between the worst (0% in the detection task and 50% in the forced-choice discrimination task) and the best possible performance (100% for both tasks).

Participants started the titration trials with a high contrast stimulus and, every 20 trials, target contrast and the degree of line tilting were adjusted (in steps of 0.07 Michelson contrast and 1° of tilting, respectively) to converge to the preestablished criteria. The experiment started once performance levels reached those criteria. Throughout the experiment, stimulus parameters were automatically adjusted every 20 trials to maintain these titration levels.

Each block consisted of 200 trials, including 40 trials in which the target was absent. In half of the trials, a short burst of 4 TMS pulses was applied to the right FEF (active TMS trials) so that the last pulse of each burst was always delivered 16 ms before target onset. In the other half (sham TMS trials) the same short burst was delivered by a second TMS coil placed next to the stimulation site, with the coil surface perpendicular to the head surface, preventing the magnetic field from reaching the skull and stimulating the brain. The order of active and sham TMS trials was randomized across trials. Participants were allowed to take a short break every 40 trials and at the end of each sub-block received feedback on the screen about their performance and eye movement rates.

In two groups of participants, we explored the effects of two different stimulation frequencies, high-beta (30 Hz) and gamma (50 Hz), on visual performance. Each group performed two blocks of trials: in the frequency-specific block, 4 TMS pulses were distributed uniformly, whereas in the non-frequency-specific block, pulses were unequally distributed over the same period of time (the first and last pulses occurred at timings identical to those in the frequency-specific block, whereas the second and third pulses were slightly anticipated and delayed respectively; Fig. 1b). The order in which participants performed the two blocks was counterbalanced across participants.

Transcranial magnetic stimulation (TMS). TMS pulses were delivered using a biphasic repetitive stimulator (Superapid 2, Magstim) with a 70-mm-diameter figure-of-eight coil (Fig. 1c). A structural T1-weighted MRI scan (3T Siemens MPRAGE, flip angle = 9° , TR = 2300 ms, TE = 4.18 ms, slice thickness = 1 mm) was acquired for every participant at the CENIR (Centre de Neuro-Imagerie de Recherche) MRI center (Salpêtrière Hospital, Paris). The right FEF region was localized on each individual MRI using averaged Talairach coordinates $x = 31$, $y = -2$,

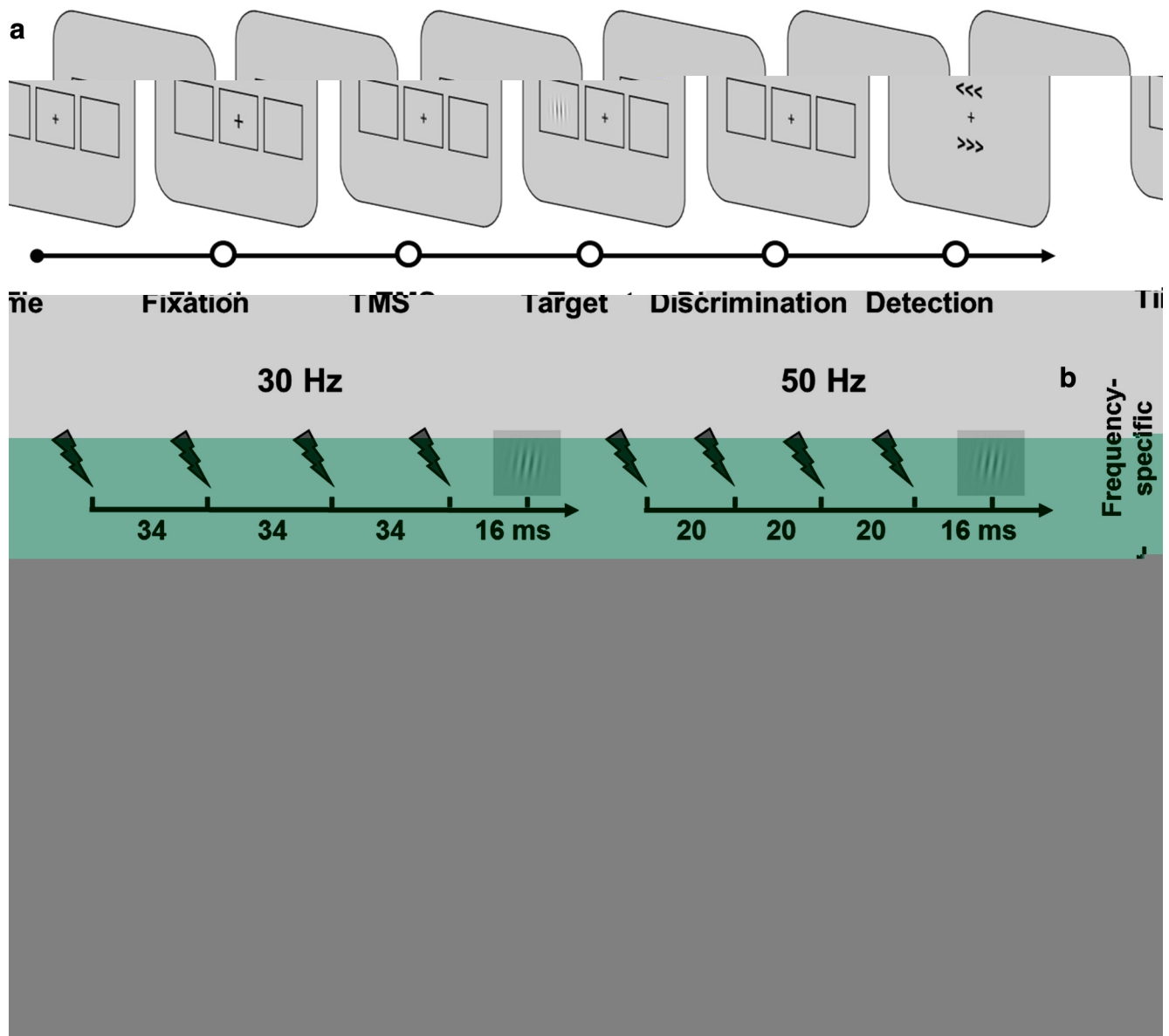


Figure 1. Experimental design. **a**, Following a period of central fixation, a low-contrast near-threshold Gabor stimulus was briefly presented within a left or right peripheral box. Participants were requested to perform a discrimination task, indicating the orientation of the Gabor lines (left/right), followed by a conscious detection task in which they reported if they had seen or not a Gabor and where (“no” or if “yes,” left/right). **b**, Schematic drawing representing the temporal distribution of the 4 pulses of each TMS burst in frequency-specific (uniform) and non-frequency-specific (nonuniform) blocks. For each stimulation frequency (30 Hz and 50 Hz), bursts used in either block were equal in duration and number of pulses. **c**, TMS coil positioning on the right FEF, displayed in a representative 3D reconstructed native MRI brain and its associated sagittal, axial and coronal brain sections.

$z = 47$ (Paus, 1996) and a 0.5 cm radius spherical region of interest (for details see Chanes et al., 2012). The final MRI was uploaded into a frameless stereotaxic system and reconstructed in 3D for its use in an online stereotaxic TMS neuronavigation system (eXimia NBS System, Nexstim).

At all times, the TMS coil was held tangentially to the skull, with its handle oriented $\sim 45^\circ$ in a rostral-to-caudal and lateral-to-medial orientation, i.e., approximately parallel to the central sulcus. Coil position was tracked online throughout the experiments and kept steady within an area of ~ 2 mm radius from the targeted site. The representation of the right primary motor cortex (M1) of the abductor pollicis brevis muscle was located and the left and right motor thresholds were determined as the TMS intensity yielding thumb twitching responses in $\sim 50\%$ of the attempts.

For all interventions, stimulation intensity was set up at 45% of the TMS machine maximal output. Nonetheless, in some participants such a level had to be slightly decreased to abolish temporal and facial muscle

involuntary activations, blinks, or other types of facial sensations induced by magnetic field spread. Before the experiment, we verified on each participant that none of the TMS FEF patterns used induced contralateral motor activations on forearm or hand muscles. The average intensities at which participants were stimulated were 44.3% (SD 1.5%) and 44.9% (SD 0.5%) of the maximum machine output for the 30 and 50 Hz bursts groups, respectively (i.e., $72 \pm 13\%$ and $74 \pm 14\%$ of their individual motor thresholds).

Statistical analyses. Outcome measures (perceptual sensitivity and response criterion for the conscious detection task and accuracy for the discrimination task) of each group (30 and 50 Hz) were subjected to a $2 \times 2 \times 2$ repeated-measures ANOVA with block (frequency- and non-frequency-specific), target location (left and right visual field), and TMS condition (active and sham) as within-participant factors. The same ANOVA was performed for trials in which participants reported to have seen the target but incorrectly determined its location (error trials), which were eliminated from the analyses, to exclude any potential effect

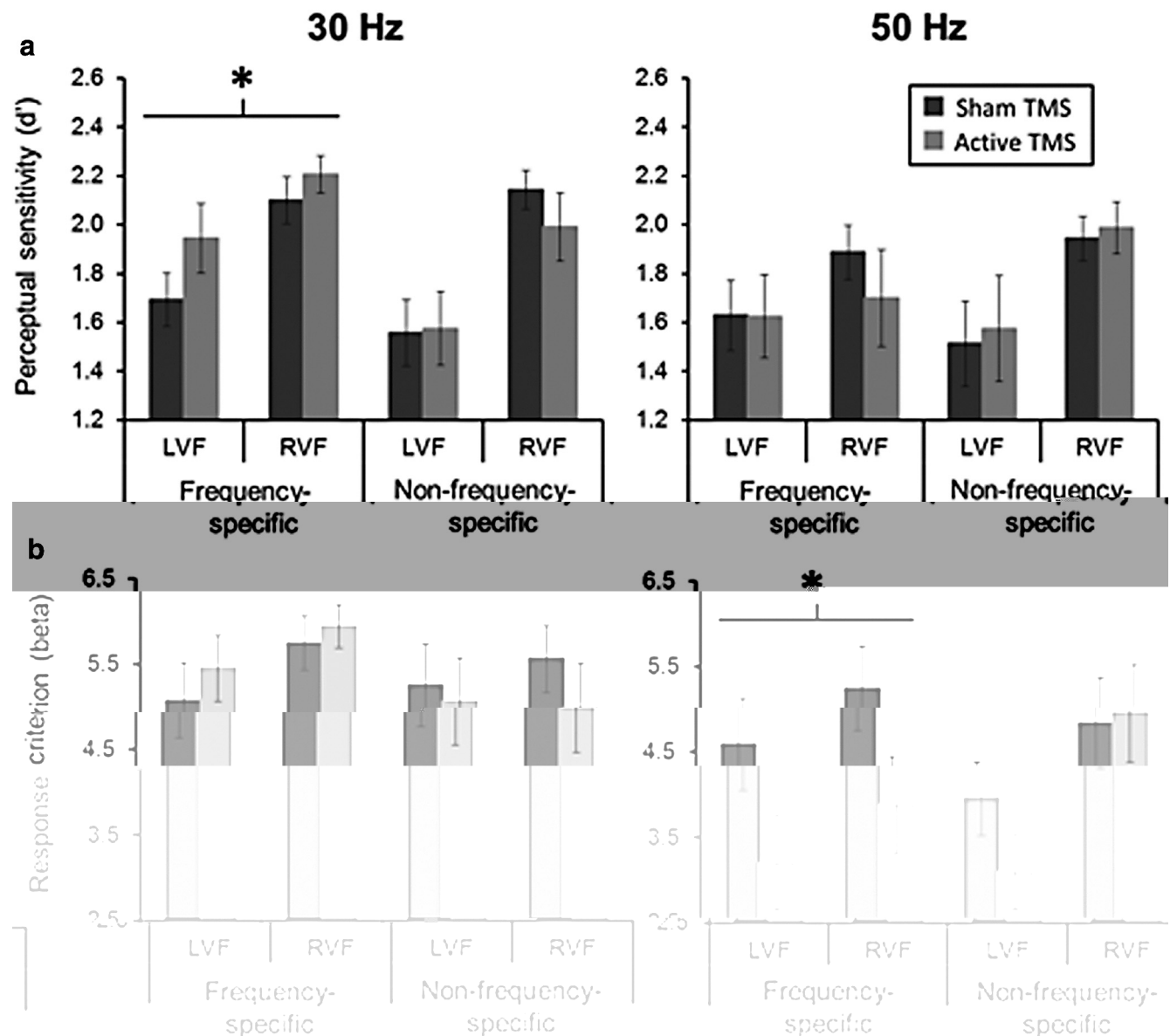


Figure 2. Impact of neurostimulation bursts at 30 and 50 Hz on conscious visual detection measures. *a, b*, Series of histograms displaying the effects of active (light gray) or sham (dark gray) frequency-specific and non-frequency-specific TMS bursts on perceptual sensitivity (*a*) and response criterion (*b*) values for each of the two TMS frequencies tested. Data are presented for targets displayed in the contralateral (left) and ipsilateral (right) visual fields (LVF and RVF, respectively) with regards to the stimulated right FEF region. Notice that active 30 Hz TMS bursts (but not their non-frequency-specific associated bursts) enhanced perceptual sensitivity (d') compared with sham TMS patterns. Neither uniform 50 Hz bursts nor their associated non-frequency-specific patterns modulated this outcome measure. In contrast, active 50 Hz TMS bursts (but not its associated non-frequency-specific burst) relaxed response criterion for active TMS bursts compared with sham. No significant criterion differences were observed either for 30 Hz TMS bursts or for their associated non-frequency specific patterns. Asterisks indicate statistically significant differences for active versus sham TMS conditions.

of TMS in such trials. Finally, the factor group (30 and 50 Hz) was implemented as between-participant factor in a general ANOVA with the same within-participant factors described above.

Results

One participant was excluded from the analyses in the 30 Hz group because broke fixation in >50% of the trials. Trials in which participants broke fixation were eliminated from the analyses (8% and 5% for the 30 and 50 Hz groups, respectively). Moreover, error trials were also eliminated (3% and 7% of seen targets for the 30 and 50 Hz groups, respectively). The repeated-measures ANOVA for errors did not yield any significant main effects or interactions, indicating that those were similar across conditions. The average number of trials per participant used in

the analyses of each experimental condition ranged between 35 and 38 (mean \pm SD: 36 ± 4). In the discrimination task, participants' general accuracy was 63% and 64% for the 30 Hz and 50 Hz groups, respectively. As expected, it was high when they reported to have seen the target (75% and 76%, respectively), and it remained at chance levels when they reported not to have seen it (50% for both groups).

Our data revealed frequency-specific contributions of FEF activity to visual performance (Fig. 2; Table 1). For the conscious detection task, active TMS bursts delivered at 30 Hz, but not at the matched non-frequency-specific patterns, improved participants' perceptual sensitivity (significant interaction between block and TMS condition, $F_{(1,12)} = 6.07$, $p = 0.030$). Scores were higher for

Table 1. Summary of main statistical effects and interactions of the different neurostimulation patterns on conscious visual detection

Group	Main effects and interactions	Perceptual sensitivity (d')		Response criterion (beta)	
		F	p	F	p
30 Hz	Block	6.328	0.027*	0.715	0.414
	Side	10.978	0.006*	1.770	0.208
	TMS	0.576	0.463	0.056	0.816
	Block \times Side	1.219	0.291	1.584	0.232
	Block \times TMS	6.072	0.030*	3.897	0.072
	Side \times TMS	2.178	0.166	1.055	0.325
	Block \times Side \times TMS	0.013	0.911	0.045	0.836
50 Hz	Block	0.229	0.641	0.002	0.968
	Side	2.180	0.164	8.069	0.014*
	TMS	0.048	0.830	7.948	0.014*
	Block \times Side	1.666	0.219	1.005	0.334
	Block \times TMS	1.776	0.205	6.418	0.025*
	Side \times TMS	0.866	0.369	0.486	0.498
	Block \times Side \times TMS	0.288	0.601	0.973	0.342

All statistically significant main effects and interactions (repeated-measures ANOVA) are indicated in the table by an asterisk (* $p < 0.05$). In addition to the significant interaction between block and TMS condition reported, for 30 Hz TMS patterns and its associated non-frequency-specific bursts: perceptual sensitivity was higher for targets displayed to the right than to the left visual field ($F_{(1,12)} = 10.98, p = 0.006$) and for frequency-specific (or uniform) blocks than for non-frequency-specific (or non-uniform) blocks ($F_{(1,12)} = 6.33, p = 0.027$). For the 50 Hz TMS pattern (and their corresponding non-frequency-specific or non-uniform bursts), in addition to the significant interaction between block and TMS condition reported, response criterion was more relaxed for targets displayed to the left than to the right visual field ($F_{(1,13)} = 8.07, p = 0.014$) and with active than sham TMS bursts ($F_{(1,13)} = 7.95, p = 0.014$).

active than for sham TMS only when pulses were uniformly delivered at 30 Hz (planned comparison active vs sham for the frequency-specific block: $F = 5.55, p = 0.036$), but not when non-uniform patterns were used (planned comparison active vs sham for the non-frequency-specific block: $F < 1$) (Fig. 2*a*, left). Moreover, no significant main effects or interactions were observed for the response criterion (Fig. 2*b*, left). In the discrimination task, no significant modulations of accuracy were observed in any of the blocks.

On the other hand, TMS bursts delivered at 50 Hz and their corresponding non-frequency-specific patterns proved unable to modulate perceptual sensitivity (d') in the conscious detection task (Fig. 2*a*, right). However, the uniform pattern shifted response criterion (significant interaction between block and TMS condition, $F_{(1,13)} = 6.42, p = 0.025$). Active 50 Hz TMS bursts decreased the strictness of participants' response criterion compared with sham TMS (planned comparison active vs sham for the frequency-specific block: $F = 13.37, p = 0.003$), whereas no significant differences in response criterion were observed when TMS bursts were delivered at their associated non-frequency-specific pattern (planned comparison active vs sham for the non-frequency-specific block: $F = 1.05, p = 0.325$) (Fig. 2*b*, right). In the discrimination task, no main effects or interactions were observed.

Finally, the significant interaction between group \times block \times TMS condition for both perceptual sensitivity ($F = 6.84, p = 0.015$) and response criterion ($F = 10.14, p < 0.01$) when group (30 and 50 Hz) was integrated as between-participant factor in a general ANOVA emphasizes the frequency specificity of the TMS impact.

Discussion

Our findings shed novel light on the oscillatory basis underlying visual detection behavior for near-threshold stimuli and suggest distinct modulatory roles for high-beta and gamma frontal activity in visual performance.

Frontal 30 Hz TMS bursts impacted perceptual sensitivity (d') in a conscious visual detection task, whereas 50 Hz TMS patterns yielded changes in response criterion. Beta oscillations from the

FEF have been previously correlated with modulations of visual performance (Gross et al., 2004; Donner et al., 2007), and we thereby show here that such activity could be causally linked to these behavioral effects. These oscillations may reflect reverberant activity within and among visual, frontoparietal and frontal motor cortices (Engel and Fries, 2010), which might facilitate the accumulation and maintenance of sensory evidence for decision-making (Donner et al., 2007; Siegel et al., 2011). Importantly, our data provide direct proof that the processing of visual sensory evidence could be episodically enhanced by an extrinsic source of neural synchronization, such as TMS, tuned to a specific oscillation frequency.

Patterns at 50 Hz over the right FEF specifically decreased response criterion when detecting faint near-threshold stimuli. This finding is consistent with prior work showing a correlation between prestimulus gamma-band oscillations in occipital regions and decision biases (Wyart and Tallon-Baudry, 2009). We now extend this result to frontal regions, and, most importantly, we hypothesize a causal contribution of gamma-band oscillations to such processes. The modulation of these phenomena by stimulus features reported previously suggests that oscillatory activity at this frequency band is likely to reflect sensory evidence (Frien et al., 2000; Siegel and König, 2003; Kayser and König, 2004; Hall et al., 2005; Henrie and Shapley, 2005; Hoogenboom et al., 2006; Liu and Newsome, 2006; Vidal et al., 2006; Siegel et al., 2007; Berens et al., 2008; Wyart and Tallon-Baudry, 2008, 2009). Accordingly, we hypothesize that the induction of a brief low-gamma pretarget pattern on a higher cortical region, such as the right FEF, holding connections with the visual cortex, may have been encoded as sensory evidence, and thus favored a conscious affirmative detection response ("Yes I saw it") over a negative one ("No I did not see it") for near-threshold targets, independent of stimulus presence, hence decreasing the strictness of the response criterion.

The double dissociation observed between stimulation frequency (30 Hz vs 50 Hz bursts) and behavioral outcome measure (perceptual sensitivity vs response criterion), together with the lack of behavioral modulations when the same activity (equal number of TMS pulses delivered across the same interval at identical stimulation intensity) was induced by a slightly different TMS pattern indicate that the observed effects are a specific consequence of stimulation frequency, rather than depend on the total amount of activity induced within a critical time window. Furthermore, none of our interventions proved able to modulate the visual discrimination task, suggesting that the induced activity might not impact visual performance at a purely perceptual level but could rather operate on conscious access. Alternatively, the discrimination task could not have been modulated simply because it might require more refined processing and accumulation of more evidence.

In sum, our results provide causal evidence that characteristic spatiotemporal activity patterns induced by neurostimulation to the same cerebral region can yield exquisitely distinct behavioral outcomes such as increases of visual sensitivity and decreases of response criterion. Such evidence may reflect a general brain mechanism to multiplex functions within the same neural substrate (Thut et al., 2012). Findings coherent with this notion have been reported for parietal TMS bursts delivered at lower stimulation frequencies (Romei et al., 2010, 2011). Similarly, recordings in non-human primates have provided correlational evidence of enhanced gamma frequency synchrony between frontal and posterior parietal regions during exogenous attention in a pop-out visual detection task, and synchrony increases at the high-beta range between these

same areas during endogenous attentional orienting, as tested in a visual search paradigm (Buschman and Miller, 2007, 2009). Similar to the current data, such evidence in the field of attentional orienting supports the hypothesis that characteristic synchronization patterns emerging from the FEF may underlie different cognitive processes, leading to different behavioral outcomes.

Finally, our data show that perceptual sensitivity in healthy participants can be episodically enhanced by an extrinsic source of neural synchronization tuned to a specific frequency and support future uses of non-invasive neurostimulation to probe and manipulate oscillatory phenomena in the human brain from circumscribed cortical regions. Furthermore, pathological conditions involving specific alterations of cerebral oscillations (Thut et al., 2012) associated with impaired cognitive performance could potentially benefit from the use of frequency-tailored neurostimulation to locally manipulate activity and restore the characteristic oscillation frequencies of the healthy system.

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