



Fronto-tectal white matter connectivity mediates facilitatory effects of non-invasive neurostimulation on visual detection



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ABSTRACT

The causal ability of pre-target FEF activity to modulate visual detection for perithreshold stimuli has been recently demonstrated in humans by means of non-invasive neurostimulation. Yet in spite of the network-distributed effects of these type of techniques, the white matter (WM) tracts and distant visual nodes contributing to such behavioral impact remain unknown. We hereby used individual data from a group of healthy human subjects, who received time-locked pulses of active or sham Transcranial Magnetic Stimulation (TMS) to the right Frontal Eye Field (FEF) region, and experienced increases in visual detection sensitivity. We then studied the extent to which interindividual differences in visual modulation might be dependent on the WM patterns linking the targeted area to other regions relevant for visuo-attentional behaviors. We report a statistically significant correlation between the probability of connection in a right fronto-tectal pathway (FEF-Superior Colliculus) and the modulation of visual sensitivity during a detection task. Our findings support the potential contribution of this pathway and the superior colliculus in the mediation of visual performance from frontal regions in humans. Furthermore, we also show the ability of a TMS/DTI correlational approach to contribute to the disambiguation of the specific long-range pathways driving network-wide neurostimulatory effects on behavior, anticipating their future role in guiding a more efficient use of focal neurostimulation.

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Introduction

Visual systems translate information from the real world into sophisticated bioelectrical patterns, which can be used thereafter to build a neural representation of our environment. It is well known that such function is strongly modulated by bilaterally distributed fronto-parietal networks in charge of orienting attention to specific regions of the space, facilitating the detection and discrimination of visual stimuli (Cameron et al., 2002; Carrasco et al., 2000, 2001; Yeshurun and Carrasco, 1999). Such operations are essential for the selection of behaviorally crucial targets to be attended in a world rich in distractors, without being overwhelmed by numerous and diverse sources of information.

Fronto-parietal visuo-attentional networks are classically divided into a bilateral dorsal system, linking the Frontal Eye Fields (FEF) and the Intra-parietal Sulcus (IPS), involved in the orienting of attention in

space (Beauchamp et al., 2001; Chica et al., 2011; Corbetta and Shulman, 2002; Shulman et al., 2010), and a ventral right-lateralized system between the middle and the Inferior Frontal Gyrus (MFG/IFG), and the Temporo-Parietal Junction (TPJ), responsible for the reorientation of attention during unexpected events (Chica et al., 2011; Corbetta and Shulman, 2002; Shulman et al., 2010). Importantly, neuroimaging data (Nobre et al., 1997; Petit et al., 2009), non-invasive neurostimulation evidence (Grosbras and Paus, 2003; Hilgetag et al., 2001; Thut et al., 2005), and clinical observations (Bartolomeo et al., 2012) strongly support a right hemisphere dominance in visuo-spatial attention, and demonstrate the ability of such right-hemisphere systems to influence visual perception for targets in both visual hemifields (Grosbras and Paus, 2003; Chanes et al., 2012).

White matter (WM) connections established between nodes of this network have been thoroughly studied and remain essential to understand its contributions to spatial attention and perception. Intracortical microstimulation and tracing studies carried out in the non-human primate brain have shown that the FEF is highly connected to the superior and ventral portions of the parietal lobe and to caudal regions of the superior temporal cortex (Huerta et al., 1987; Stanton et al., 1995). Similarly in humans, this network is underlain by a rich set of anatomical WM projections which in homology to non-human primates have

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been recently identified as the three branches of the Superior Longitudinal Fasciculus (Thiebaut de Schotten et al., 2012), linking key regions of the frontal and the posterior parietal lobes (Thiebaut de Schotten et al., 2011; Umarova et al., 2010). Finally, connections between fronto-parietal systems and subcortical structures such as the pulvinar nucleus of the thalamus and the superior colliculus (SC) in the midbrain are also important and contribute to both overt and covert attentional deployment (Shipp, 2004).

Engaged exogenously (i.e., by reflexively capturing attention) or guided endogenously (i.e., according to feature-based instructions), these circuits have the ability to modulate the gain of retinal incoming signals to cortical (Reynolds and Chelazzi, 2004; Reynolds and Desimone, 2003; Reynolds et al., 2000) and subcortical structures (Gattass and Desimone, 1996; O'Connor et al., 2002; Schneider and Kastner, 2009; Wurtz and Goldberg, 1972), and impact visual processing. Indeed, studies in non-human primates have proven the potential of FEF microstimulation, alone or in combination with bottom-up visual inputs to modulate activity in visual areas (Ekstrom et al., 2009; Reynolds and Chelazzi, 2004) and influence visual performance (Moore and Fallah, 2004). Similarly in humans, Transcranial Magnetic Stimulation (TMS), a tool which induces pattern-dependent local and transynaptic effects through long-range connectivity (Valero-Cabré et al., 2005, 2007) has shown the ability to elicit in the FEF and IPS regions brief (Grosbras and Paus, 2002, 2003; Ruff et al., 2006; Silvanto et al., 2006) and transient (Hilgetag et al., 2001; Thut et al., 2005) modulations of visual behaviors.

In a recent report, we demonstrated that single-pulse TMS stimulation delivered to the right FEF had the ability to improve the detection but not the discrimination of low-contrast near-threshold visual stimuli (Chanes et al., 2012). This result strongly supports the notion that vision can be non-invasively manipulated and enhanced in humans. However the underlying circuitry linking the targeted regions, the right FEF, and other brain locations contributing to such visual ameliorations are not easy to disambiguate on the basis of differences in the behavioral patterns recorded under the causal influence of neurostimulation. Using a hypothesis-driven approach, we correlated individual MRI diffusion data (Behrens et al., 2007) from a set of four anatomically plausible tracts emerging from the stimulated right FEF and known to be involved in the orienting of spatial attention, and visual performance outcomes modulated by TMS. A preceding Tract-Based Spatial Statistics (TBSS) data-driven analysis was employed in an attempt to identify WM voxel clusters with diffusion measures correlated to visual performance outcomes. Overall, we aimed to identify the WM pathways which would best explain individual effect differences in visual sensitivity for our population of right FEF neurostimulated participants (Chanes et al., 2012) that could be most likely associated with our patterns of behavioral effects. We hypothesized that the WM pathways significantly correlated with neurostimulation-driven outcomes would involve brain sites linked to the FEF, with processing features and abilities compatible with the characteristics of the modulated visual behaviors.

Material and methods

Participants

The TMS data used in the current manuscript were extracted from two experiments of a recently published behavioral-TMS data set (Chanes et al., 2012). This study included 13 human subjects (5 males and 8 females; mean age, 23.8 ± 3 years; range 18–28 years). All these participants provided informed written consent and were compensated for their participation. They all took part voluntarily in the study, and were naïve to both, the purpose of the experiment and the uses of TMS. The protocol was reviewed by the Inserm (Institut National de la Santé et la Recherche Scientifique) ethical committee and approved by an Institutional Review Board (CPP Ile de France 1).

Behavioral paradigm and TMS stimulation

The visual paradigm used in both experiments worked as follows. A fixation point was displayed in the center of the screen, along with three black square boxes, one central and two lateral ones. The target consisted of a *Gabor* stimulus, which could appear at the center of one of two lateral rectangular place holder for a brief period of time (33 ms). The *Gabor* bars were tilted 1° to 10° to the left or to the right (corresponding 0° to their vertical orientation). Single TMS pulses were delivered 80 ms prior to target onset on the right FEF. This region was individually labeled on each individual MRI volume using averaged Talairach coordinates $x = 31$, $y = -2$, $z = 47$ (Paus, 1996). This location was confirmed on each participant's MRI native space by a procedure based on the elicitation of saccade preparation delays under the impact of single TMS pulses on this site (Chanes et al., 2012; Grosbras and Paus, 2002, 2003; Ro et al., 2002; Thickbroom et al., 1996). In Experiment 1 (pre-target onset TMS pulses alone), after a variable fixation period of time (1000–1500 ms), the central fixation cross became slightly bigger for 66 ms and following an Interstimulus Interval (ISI) of 233 ms a target was displayed for 33 ms within one of the two lateral boxes. Single TMS pulses were delivered on the right FEF 80, 100 or 140 ms prior to the target onset. Active TMS pulses were randomly interleaved by an equal number of sham single pulses delivered by a second TMS coil with its surface located perpendicular to the head surface, next to the right FEF site. The experiment consisted of 600 trials, including 120 target-absent trials. In Experiment 2 (pre-target onset spatial cues combined with single TMS pulses), the paradigm was kept identical, except that a peripheral cue consisting in a black dot (1.5° diameter) was presented for 66 ms in the upper outer corner of one of the two lateral square place holder to orient the attention of the participant to that location (Fig. 1). After an identical ISI, a *Gabor* appeared at the center of the cued (valid trials) or uncued (invalid trials) lateral box. The cue was predictive about the location of the subsequent target (75% valid and 25% invalid trials). For this second experiment, single TMS pulses were delivered 80 ms prior to target onset and the session consisted in 800 trials, including 160 target-absent trials.

In both experiments, participants were first required to determine the orientation of the *Gabor* bars (*categorization* task) as fast and as accurately as possible. They were encouraged to respond to every trial within a window of 2000 ms, and forced to guess a response, even when the target was not present or they did not consciously perceive it. Secondly, they were requested to report whether they perceived the *Gabor* in the left, in the right, or they did not see it (*detection* task). Categorization performance was analyzed through accuracy (correct grating orientation categorization) and reaction time for correctly reported targets. Perceptual sensitivity (d') and response bias (β) used in Signal Detection Theory (SDT) served to assess the modulation of visual detection in the second response. Subjects were requested to keep their gaze on the fixation cross throughout the trial. Correct fixation was controlled by an eye-tracker system. Target contrast was adjusted prior and throughout the task so that ~62% of the displayed targets were reported (*detection* task) and 65 to 85% of the correctly reported targets were also correctly discriminated (*categorization* task) (see Chanes et al., 2012 for details).

MRI acquisition

Prior to the TMS study, diffusion tensor MRI scans were obtained in all thirteen participants on a 3 Tesla MRI scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany) located in the CENIR (Centre de Neuro-Imagerie de Recherche) at the Hôpital de la Pitié Salpêtrière, in Paris (France). Using a 12-channel array coil and a maximum gradient strength of 28 mT/m, diffusion weighting was isotropically distributed along 64 directions. Note that high angular resolution of the diffusion weighting directions yields robust probability density estimation by

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