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Lorena Chanes Puiggros

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Frontal and parietal contributions to visual perception in humans

Lorena CHANES

Directeur:
Dr. Antoni VALERO-CABRE

Membres du jury :

Dr. Marisa CARRASCO Examineur
Dr. Karim JERBI Rapporteur
Dr. Michel LE VAN QUYEN Examineur
Dr. Pascale PRADAT-DIEHL Présidente du jury
Dr. Juha SILVANTO Rapporteur
Dr. Antoni VALERO-CABRE Directeur de thèse
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Mais le seul qui ait tenu le coup,
Qui n'ai jamais viré de bord,
Mais viré de bord,
Naviguait en père peinard
Sur la grand-mare des canards,
Et s'app'lait Les Copains d'Abord
Les Copains d'Abord.
(Geroges Brassens)
SUMMARY

Frontal and parietal areas have been shown to subtend different cognitive processes such as attentional orienting, decision making and access to consciousness, with bearing on visual performance. In spite of prior evidence supporting an implication of those regions in visual cognition, their contributions to the processing of low-contrast unmasked stimuli and the characteristic spatiotemporal activity patterns underlying them remain to be fully explored and causation is lacking. We here addressed a thorough exploration of such contributions in humans, with an emphasis on the dynamics of neural activity and visual performance enhancements as probed by patterns of noninvasive manipulation of local brain oscillatory activity. To this end, we tested in healthy participants the effects of either single pulses or short bursts of active vs. sham transcranial magnetic stimulation (TMS), delivered to the frontal eye field (FEF) and the intraparietal sulcus (IPS) prior to the presentation of a lateralized low-contrast near-threshold Gabor stimulus, on the visual discrimination and conscious detection of such stimulus. In Chapter II we show that single TMS pulses delivered to the right FEF alone or in combination with visuo-spatial cues have the ability to increase perceptual sensitivity, effects that proved strongly modulated by cue validity. In Chapter III we report that induced pre-target high-beta (30 Hz) activity in this same region selectively enhances perceptual sensitivity (d’) whereas gamma band (50 Hz) bursts selectively shift response criterion (beta). This result shows that neural oscillations could be a general mechanism to multiplex functions, with specific behavioral effects, in the same region or network. In Chapter IV we provide evidence of stochastic facilitation of perceptual performance, showing perceptual sensitivity
enhancements by the induction of neural noise to the left FEF, and demonstrate that the left and right hemispheres modulate visual performance through different coding strategies possibly reflecting different cognitive processes. In *Chapter V* we show that the effects of right-FEF high-beta activity on perceptual sensitivity are phase independent and that additional perceptual phase-dependent effects can be observed. Finally, in *Chapter VI*, we report for the right IPS similar frequency-specific effects to the ones observed in the right FEF as well as additional perceptual modulations when the pulses are delivered in a short time window. Our findings contribute to better substantiate the oscillatory basis of visual cognition and its associated behaviors and to set the stage for the development of novel therapies based on noninvasive manipulation of dysfunctional brain oscillatory activity.
Les aires cérébrales frontales et pariétales sont impliquées dans différents processus cognitifs importants pour la performance visuelle, tels que l’attention ou la conscience. Malgré les preuves existantes en faveur d’une implication de ces régions dans la cognition visuelle, leurs contributions dans le traitement de stimuli non masqués de faible contraste ainsi que l’activité spatio-temporelle sous-tendant ces contributions restent largement inexplorées, tout particulièrement en termes de causalité. Nous avons mené une exploration approfondie de ces contributions chez l’humain, en mettant l’accent sur la dynamique de l’activité neurale et les améliorations perceptives potentielles qui peuvent résulter de la manipulation non invasive de l’activité cérébrale. À cette fin, nous avons testé chez des sujets sains les effets d’impulsions simples ou de rafales courtes de stimulation magnétique transcrânienne (SMT) réelle versus fausse, délivrée sur le champ oculomoteur frontal ou le sillon intrapariétal avant la présentation d’un filtre de Gabor de faible contraste, sur la discrimination et la détection consciente de ce filtre de Gabor. Nos résultats montrent que chez l’humain, la distribution spatio-temporelle de l’activité frontale et pariétale joue un rôle causal dans la performance visuelle. Nos recherches contribuent à mieux comprendre les bases oscillatoires de la cognition visuelle et les comportements associés et à préparer le terrain pour le développement de nouvelles thérapies basées sur la manipulation non-invasive de l’activité cérébrale oscillatoire avec, pour objectif ultime, l’amélioration des pathologies neuropsychiatriques.
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Chapter I

Introduction and Aims
At every moment of our lives, our senses are hit by much more information than we can treat. To succeed in using sensory inputs to act, cognitive processes such as attentional orienting help us prioritize those data that are behaviorally meaningful, selecting stimuli involuntarily because of their physical saliency or voluntarily according to their granted relevance to achieve our behavioral goals in a given context. Moreover, information that accesses consciousness will be able to be largely stored and strategically used and, in order to produce goal-directed behavior, evidence will need to be flexibly translated into motor actions through decision-making processes. All these operations shape the way we act and perform.

In this introduction we will present a brief overview of the current knowledge on the neural basis of visual perception, and some of the processes relevant for perceptual performance such as attention and conscious access. We will then address how noninvasive neurostimulation techniques can be used to manipulate activity in different brain regions and their associated networks and provide new insights on their role and processing features.

I.I. Visual perception

Vision is one of the main senses in humans and it has been extensively studied in virtually all organisms. In order to produce a visual percept, light reaches the retina, which contains a large number of photoreceptors. These photoreceptors convert this incoming radiation into electrical signals that are conveyed to the brain through the optic nerve. Most part of the retinal ganglionar cell axons (about 90%) relay on the lateral geniculate nucleus (LGN) of the thalamus to then reach the primary visual cortex (V1 or striate cortex). A few projections (about 10%) relay on the superior colliculus in the midbrain (Perry and Cowey 1984), which is known as
the indirect retino-tectal pathway. The superior colliculus influences the visual and posterior parietal regions indirectly through the pulvinar nucleus of the thalamus and receives modulatory projections from the primary visual cortex (Shipp 2004).

The primary visual cortex is retinotopically organized (Hubel and Wiesel 1959) and devoted to the processing of basic visual features, as for example spatial frequency (De Valois et al. 1982a; Maffei and Fiorentini 1973; Tootell et al. 1981), line orientation (De Valois et al. 1982b) and stimulus contrast (Hawken and Parker 1984). From V1 information is transmitted to the extrastriate cortex (V3, V4 and MT/V5), where higher order processing takes place (Orban 2008). Lesions to V1 involve a decrease of visually evoked activity in extrastriate visual areas and temporal cortices (Gross 1991; Rocha-Miranda et al. 1975). Moreover, visual perception is thought to involve feedback and feed-forward activations within and amongst V1 and higher order visual areas (Hupe et al. 1998).

Two pathways have been identified for the flow of information from the primary visual cortex to higher order areas: the dorsal and the ventral streams. The ventral stream (also known as the “what” stream) travels from the occipital to the inferior temporal cortex, including V2 and V4 and it is associated with the visual recognition and categorization of objects and faces (Kanwisher et al. 1997; Kourtzi and Kanwisher 2000). Lesions to the ventral visual stream result in visual agnosias (Ffytche et al. 2010). For example, in the early 90s an influential study described the case of a patient with a lesion of the ventral stream who presented a severe visual form agnosia (Goodale et al. 1991). This patient, however, had preserved guidance of hand movements with regards to objects the qualities of which (e.g. orientation) he failed to perceive. This preserved visuomotor ability would be coded in the dorsal visual stream. Indeed, the dorsal stream (also known as the “where”/“how” stream) is
associated with spatial localization and visuomotor control and projects from the occipital to the posterior parietal cortex, including areas V2, V3a, middle temporal (MT) and middle superior temporal (MST) cortices. Lesions to the dorsal visual stream result in a variety of cognitive dysfunctions including spatial neglect (Heilman et al. 1993), which involves inability to perceive and/or attend to stimuli contralateral to the lesion, and optic ataxia (Battaglia-Mayer and Caminiti 2002; Pisella et al. 2000; Pisella et al. 2009), which involves failure to integrate visual and motor information and thus to perform adapted visuomotor plans. The two streams are thought to interact to contribute to action and perception (Goodale and Westwood 2004; Milner et al. 2003; Westwood and Goodale 2003). For example, a patient with a bilateral lesion of the ventral stream presenting visual form agnosia, has impaired ability to adjust hand aperture to different object sizes (Goodale et al. 1994) and increased pointing errors to remembered target positions (Milner et al. 1999) when the action is delayed for a few seconds. Conversely, dorsal-stream lesion patients with optic ataxia improve when there is a delay between target and movement onset (Himmelbach and Karnath 2005; Milner et al. 2003; Milner et al. 1999; Revol et al. 2003). It has been suggested that such impairment and enhancement are mediated by the spared stream.

I.II. Neural bases of cognitive processes involved in visual performance

Cognitive processes such as attention and conscious access shape our performance with regards to sensory stimuli. In the last decades, research at different levels, from invasive single neuron recordings in nonhuman primates to noninvasive neuroimaging studies, have focused on mapping the brain systems of these complex processes, which tend to overlap at least partially and thus are difficult to dissect out.
I.II.1. Neural bases of visuo-spatial attention

Attentional orienting is crucial for an adaptive interaction of organisms with their environment, allowing them to pursue their behavioral goals while being capable of responding to unexpected but behaviorally relevant events. For example, the allocation of attentional resources in a particular region of the space improves the processing of stimuli presented in such region (Carrasco et al. 2000; Yeshurun and Carrasco 1998). Attention can be oriented in space either endogenously (voluntarily or top-down) or exogenously (involuntarily or bottom-up), and both types interact dynamically to allow appropriate perceptual behavior. In the mid-eighties, Posner and collaborators made popular the cue-target paradigm, which since then has been widely used to study visuospatial attention (Posner 1980; Posner et al. 1980; Posner et al. 1984). In this paradigm, participants have to detect or discriminate, as fast and as accurately as possible, a visual target presented on a screen that is preceded by a spatial cue displayed either centrally (e.g. an arrow) or peripherally (e.g. a salient dot near one of the potential locations of the target) and informative or not about target location. Peripheral non-informative cues engage exogenous attention, since the cue captures attention by its physical saliency, whereas central informative cues can be used strategically by participants to endogenously orient their attention towards the expected location of the target. All these cues typically decrease reaction times when they correctly predict the location of the target (valid trials) as compared to when target location is incorrectly predicted (invalid trials).

Early evidence from neurological patients and physiological studies monkeys has indicated the importance of frontal and parietal regions for visuospatial attention (e.g. (Goldberg and Bruce 1985; Mesulam 1981; Posner et al. 1984)). More recently,
investigators have searched for the neural basis of spatial attention in the healthy human brain using correlational techniques such as functional MRI (fMRI). One of the first studies to dissociate the brain activity related to attention from the activity related to the processing of the target revealed the superior frontal, inferior parietal and superior temporal cortices as the regions activated by the cues (Hopfinger et al. 2000). Taken together, neuroimaging studies have led to the proposal of two cortical networks that are involved in visuospatial attention (Corbetta et al. 2002). According to this model, a bilateral dorsal fronto-parietal network, including the intraparietal sulcus (IPS) and the frontal eye fields (FEF), would be in charge of orienting our attention in space. Indeed, the FEF and the IPS have been shown in humans and non-human primates to reflect the locus of attention (Armstrong et al. 2009; Bisley and Goldberg 2003; Kelley et al. 2008; Thompson et al. 1997; Thompson et al. 2005). A right-lateralized ventral network, including the temporoparietal junction (TPJ) and the inferior frontal gyrus (IFG), would be involved in the reorientation of attention towards unexpected and task-relevant events (Corbetta et al. 2008).

Recent studies have pointed out the importance of white matter tracts linking these cortical regions, in particular the superior longitudinal fascicule (SLF) and the inferior fronto-occipital fascicule (IFOF), for spatial attention. The SLF appears to present a dorsal to ventral increase in lateralization, with its dorsal-most branch (SLF I), overlapping with the dorsal attentional network, being symmetrically distributed in both hemispheres and its most ventral branch (SLF III), overlapping the ventral attentional network, being right-lateralized (Thiebaut de Schotten et al. 2011). It has also been hypothesized that the middle branch of the SLF (SLF II), overlapping with the anterior portion of the dorsal network and the posterior portion of the ventral network, would link both networks (Thiebaut de Schotten et al. 2011).
Spatial attention has also been shown to involve subcortical regions, particularly the superior colliculus (SC) and the pulvinar nucleus of the thalamus (Shipp 2004). The SC contains a retinotopic map of the external world. It receives direct input from the frontal, parietal and visual cortices and it is thought to be involved in both endogenous and exogenous attention (Fecteau et al. 2004; Kustov and Robinson 1996; Rafal et al. 1988). Moreover, it has recently been shown to present sustained activity in those neurons coding for the attended location (Ignashchenkova et al. 2004). The pulvinar is widely interconnected with the cortex and has been proposed to coordinate activity within multiple cortical regions (Petersen et al. 1987; Saalmann et al. 2012; Snow et al. 2009).

I.II.2. Neural bases of conscious access

In the last decades, a growing body of experimental work has revealed that sensory stimuli that do not access consciousness are however treated by the brain and can influence our behavior. As an early example, in the seventies, it was discovered that some patients with lesions to the primary visual cortex and associated visual deficits could perform over chance levels in simple tasks on stimuli presented in the blind part of his visual field where they reported not to see anything (Poppel et al. 1973; Weiskrantz et al. 1974). Weiskrantz and colleagues named this condition blindsight (Weiskrantz et al. 1974).

More recently, several investigators have studied the cerebral processing of stimuli that do not access consciousness in healthy participants using different paradigms that allow rendering stimuli subliminal and study conscious vs. unconscious processing, including near-threshold stimuli, masking, bistable images, binocular rivalry, inattentional blindness and change blindness. Using masked stimuli,
it has been shown for example that the emotional valence of subliminal stimuli can be treated by the amygdala (Whalen et al. 1998). This evidence has been supported by further data in a cortically blind patient (named G.Y.) who had massive damage to the left occipital lobe, sparing the occipital pole only, as well as a destruction of the optic radiation (Barbur et al. 1993). This patient was capable of discriminating over chance levels emotional facial expressions presented to his blind visual field (de Gelder et al. 1999) and showed activation of the amygdala (without activation of the fusiform face area) for fear vs. happy faces presented in such region (Morris et al. 2001). Moreover, studies have reported the existence of subliminal priming at different levels, visual, (Dehaene et al. 2001), semantic (Naccache and Dehaene 2001; Van den Bussche et al. 2009), and have shown that subliminal monetary incentives can influence subjects’ motivation (Pessiglione et al. 2007) indicating that subliminal information is not only treated by the brain but can also affect our behavior. Such influence is, however, potentially very limited (Dehaene and Changeux 2011; Dehaene and Naccache 2001). For example, it appears to decrease with time, as suggested by subliminal priming studies showing that the effect is observed only when the prime-to-target time is under 500 ms (Dupoux et al. 2008; Greenwald et al. 1996; Mattler 2005), and it is often unable to flexibly modulate cognitive control (e.g. (Kinoshita et al. 2008; Kunde et al. 2003). So, the brain treats sensory information that does not access consciousness and such information is able to affect our behavior.

Conscious access of sensory information is characterized by a subjective reportable experience, which constitutes an operational definition. We can consider that a sensory stimulus has gained access to consciousness when the subject is able to report it (Dehaene and Changeux 2011; Tallon-Baudry 2011). Several fMRI
studies have shown that the activation of cortical sensory regions is not sufficient for information to be conscious, but that conscious experience is often accompanied by an amplification of the activity in those regions (Polonsky et al. 2000; Williams et al. 2008), as well as fronto-parietal activations (Carmel et al. 2006; Dehaene et al. 2001). EEG, MEG and intracortical recordings have helped characterize temporally conscious experience, revealing robust conscious correlates at late stages (>300 ms) of information processing (Babiloni et al. 2006; Del Cul et al. 2007; Fernandez-Duque et al. 2003; Lamy et al. 2009; Niedeggen et al. 2001; Pins and Ffytche 2003; Quiroga et al. 2008; Sergent et al. 2005), although early correlations have also been reported (Pins and Ffytche 2003). Other studies have also suggested that consciousness is an all-or-none process (Dehaene et al. 2003; Quiroga et al. 2008; Sergent et al. 2005; Sergent and Dehaene 2004), meaning that there would be a sharp rather than continuous transition between unconscious and conscious perception.

Interestingly, the above-mentioned studies in humans are in agreement with prior monkey data. In particular, recordings from several lower and higher visual areas during binocular rivalry showed that cells in those regions increase their firing rate when their preferred stimulus is perceived, supporting the idea of a distributed neural substrate for visual awareness (Logothetis et al. 1996; Sheinberg and Logothetis 1997). A first neuronal response period is thought to reflect sensory evidence while a later response period has been shown to correlate with stimulus detection in the primary visual, inferotemporal and frontal cortices (Kovacs et al. 1995; Lamme et al. 2002; Super et al. 2001; Thompson and Schall 1999; Thompson and Schall 2000), supporting the idea of late correlates of conscious access.

Several models of conscious access have used reportability as an operational definition for consciousness. Of all of them, the *global workspace* remains one of the
most influential ones (Baars 1989). According to this model, a dominant coalition of specialized neural processors is selected amongst several that perform their operations in parallel due to its pertinence for the organism’s behavioral goals. This coalition sends its result to the global workspace, from which it can be broadcasted to the rest of the system, what would constitute conscious access. Based on this idea, the *global neuronal workspace* model proposed a neural substrate for the workspace (Dehaene and Changeux 2005; Dehaene et al. 2006; Dehaene et al. 1998; Dehaene and Naccache 2001; Dehaene et al. 2003), which included long-range axonal projection neurons, densely distributed in the prefrontal and parietal cortices, capable of conveying information to distant regions. It is the sudden ‘ignition’ of such systems what would correspond to conscious access and they would then stay in a reverberant state that would allow retaining the information. Another model for which reverberant, reentering loops are a key element is Victor Lamme’s proposal (Lamme 2006). He proposes that it is precisely the reentering loops what creates consciousness. When information arrives at V1, it rapidly progresses anteriorly and then there is reverberation and that reverberation, particularly in ventral regions, creates an integrated state in which according to Lamme the information is already conscious. For Lamme this state would correspond to phenomenal consciousness, which precedes and exceeds reportability. Then that reverberation would extend to fronto-parietal regions and we would have reportability. Another influential model, the *information integration theory* (Tononi 2008; Tononi and Edelman 1998), has focused on two general properties of conscious experience: integration (i.e. a conscious scene is unified) and differentiation or complexity (i.e., a conscious scene involves the selection of a given conscious ‘state’ among a huge repertoire). According to this model, differentiation (i.e. the availability of a rich and diverse repertoire of neural
activity patterns) would be reflected by low-voltage, fast activity characteristic of waking and REM sleep, whereas integration would result from effective and rapid reentrant interactions in the thalamocortical system. This way, there would be a large functional complex cluster of neuronal groups that would constitute, on a temporal scale under the second, a unified neural process. They named this cluster the ‘dynamic core’, which would typically include posterior and anterior corticothalamic regions. Another proposal has suggested that conscious access involves the formation of a stable coalition of neurons (similar to the above mentioned ‘dynamic core’) and the key contribution of reverberating gamma oscillations, although in later versions they emphasized a role for connections with the prefrontal cortex (Crick and Koch 1990; Crick and Koch 1995; Crick and Koch 2003; Crick and Koch 2005).

Other processes, such as decision-making, are also relevant for perceptual performance. Decision-making is a complex flexible process, e.g., the same sensory information can lead to different actions or different sensations can lead to the same action, depending on the individual’s goals (Siegel et al. 2011). Research in monkeys has provided rich evidence on the involvement of sensory, parietal and frontal activity in the encoding of sensory evidence, its accumulation over time and the planning of motor action (Glimcher 2003; Gold and Shadlen 2007; Kable and Glimcher 2009; Romo and Salinas 2003; Schall 2001). Consistently with monkey studies, fMRI studies in humans in different sensory modalities have provided proof that sensory neurons encode the representation of sensory evidence used in decision-making (Binder et al. 2004; Heekeren et al. 2004). As in monkeys, the accumulation of sensory evidence in regions like the dIPFC and the IPS also appear to occur in humans. Studies have shown that activity in the dIPFC may integrate the output from
lower-level sensory regions and use the comparison between activity of selectively
tuned neuronal populations to compute decisions (Heekeren et al. 2004; Krawczyk
2002). Finally, studies in humans have also shown, similarly to the work in monkeys,
that motor areas involved in motor response actions (e.g. the FEF in the case of an
occulomotor response) are also implicated in decision-making processes (e.g.
(Heinen et al. 2006) in the case of oculomotor reponses).

I.III. Neural dynamics of visuospatial attention and conscious access

The processes and subprocesses reviewed in the previous section involve
highly co-localized cortical networks. For example, resources within regions such as
the FEF or the IPS are involved in several operations. How do the same sets of brain
regions subtend different functions and how are these coordinated? In the last years,
the idea of dynamic functional circuits that arise to flexibly map brain functions,
investigated by means of high temporal resolution techniques at different spatial
scales (intracortical recordings, EEG and MEG), has gained weight, together with
the notion that these networks and their interactions are regulated through cerebral
oscillations (Engel et al. 2001; Salinas and Sejnowski 2001; Varela et al. 2001).
Research using these correlational techniques has helped characterize the temporal
dynamics of the perceptual relevant processes described in previous sections.

I.III.1. Neural dynamics of visuospatial attention

Local and long-range cerebral oscillations at different frequency bands, including
alpha, beta and gamma, have been related to attentional processes. In particular,
visuospatial attention has been shown in occipital and parieto-occipital cortices to
decrease alpha activity contralaterally to attended locations and increase it
contralaterally to unattended ones (Gould et al. 2011; Rihs et al. 2007; Sauseng et al. 2005; Thut et al. 2006; Worden et al. 2000). It has also been shown in visual areas that attention improves gamma oscillatory activity in humans (Doesburg et al. 2008; Tallon-Baudry et al. 2005) and monkeys (Bichot et al. 2005; Fries et al. 2001; Womelsdorf et al. 2006).

Long-range coherence between frontal, parietal and visual cortices and more specifically, increases of gamma band activity (35-51 Hz) on parieto-occipital areas by endogenous attention have been reported (Gruber et al. 1999). Also, endogenous attention in a motion direction discrimination task selectively enhanced gamma-band (35-60 Hz) synchronization between the posterior parietal cortex (PPC) and mediotemporal cortex (MT) and between the FEF and MT during the delay period for the hemisphere that processed the attended stimulus (Siegel et al. 2008). This is in accordance with non-human primates data, reflecting enhanced oscillatory coupling in the gamma band (40-60 Hz) between the FEF and V4 with endogenous attention (Gregoriou et al. 2009). In this study, the coupling appeared shifted by about 10 ms, being initiated by the FEF. Other studies in monkeys have also linked gamma- and beta-range oscillations to attention. Increases in the high-beta/low-gamma band (25-45 Hz) coherence have been observed between posterior parietal cortex (LIP) and MT neuronal populations coding for the attended location (Saalmann et al. 2007). Between frontal (FEF) and parietal (LIP) regions, activity has been shown to be enhanced at different frequency bands associated to different types of attentional orienting. Synchrony was enhanced in the beta-band (22-34 Hz) in a visual search task requiring endogenous attention, whereas in a pop-out task in which a salient stimulus captured attention exogenously, activity was enhanced at higher oscillation frequencies (35-55 Hz) (Buschman and Miller 2007). Moreover, recently, using
diffusion tensor imaging to track pulvino-cortical networks and invasive electrophysiological recordings in monkeys performing a visuo-spatial attentional task, it has been suggested that synchrony between cortical areas according to attentional demands is regulated through the pulvinar (Saalmann et al. 2012).

I.III.2. Neural dynamics of conscious access

Non-invasive neuroimaging methods have shown that conscious access in humans involves local and long-range synchronization in different frequency bands. Indeed, in humans late (>300 ms) local and long-distance synchronization increases in the gamma band (>30 Hz) across occipital, parietal and prefrontal cortices have been observed (Doesburg et al. 2009; Gaillard et al. 2009; Melloni et al. 2007; Rodriguez et al. 1999; Schurger et al. 2006; Wyart and Tallon-Baudry 2009). Intracortical recording evidence in monkeys is consistent with these findings (e.g. (Panagiotaropoulos et al. 2012) for gamma oscillations increases in the prefrontal cortex). In the beta band, decrease of local power but increase of long-range phase synchronization has been reported (12-30 Hz) (Gaillard et al. 2009; Hipp et al. 2011). Although some early increases of gamma power appearing 150-200 ms with regards to target onset have also been reported to correlate with conscious access (Fisch et al. 2009), the time window after 200 ms (300-500 ms) seems to be a more specific marker of conscious access.

Several studies have shown that gamma-band activity in the visual cortex depends on stimulus strength and features (Berens et al. 2008; Frien et al. 2000; Henrie and Shapley 2005; Hoogenboom et al. 2006; Kayser and Konig 2004; Liu and Newsome 2006; Siegel et al. 2007; Siegel and Konig 2003) and that pre-stimulus
gamma activity in lateral-occipital regions biases perceptual decisions (Wyart and Tallon-Baudry 2009). Taken together, these studies indicate that gamma frequencies in specialized regions of the sensory cortex reflect the encoding of sensory evidence during perceptual decisions (Siegel et al. 2011).

I.IV. Noninvasive brain stimulation methods and approaches

Non-invasive electrophysiological and neuroimaging methods such as EEG, MEG and fMRI have contributed important data to the neural bases of human cognition. However, these techniques lack the ability to demonstrate a causal involvement of specific brain regions and networks in different cognitive processes and behavioral outputs. Causal relationships between the contribution of specific brain areas and cognition have been traditionally established in patient lesion studies. However, factors such as the lack of focality of the damage, the high degree of interindividual variability and the interfering role of neural reorganization and behavioral compensation (which are difficult to properly control for) limit the conclusions driven by these data.

In this context, noninvasive brain stimulation technologies have emerged in the last decades as novel methods to explore causal contributions of specific brain regions and their associated networks to behavior in healthy human participants and neuropsychiatric patients. Importantly, they also allow investigators to establish causal relationships between behavioral outputs and specific brain activity patterns and states. Last but not least, these same tools can be employed to characterize the functional connectivity of brain regions, probe its sensitivity and responsiveness to perturbations and the possibility to induce lasting changes in local and network activity, which has proven therapeutic in some conditions. Several techniques (which
can be eventually combined with brain anatomical and functional methods like EEG, MEG, fMRI or DTI) have been developed in the last decades. The most established and widely used ones are transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and transcranial alternate current stimulation (tACS). Moreover, TMS and tDCS are currently used already not only for research but also for clinical purposes to treat or potentially treat different neuropsychiatric conditions (e.g. (Brunoni et al.; Loo and Mitchell 2005)). More recently, the use of other techniques such as transcranial ultrasound stimulation (TUS), transcranial pulsed current stimulation (tPCS) and transcranial random noise stimulation (tRNS) has considerably increased (Dayan et al. 2013). Although all of these techniques have the potential to provide causal evidence on the involvement of cortical regions in behavior, they differ considerably in focality, temporal resolution, portability, safety and easiness of use. For example, techniques such as tDCS and tACS can be easily used and transported and have proved safe to date, but they have a relatively poor spatial resolution and cannot be used to precisely characterize neural processes in time. On the other hand, TMS, although more difficult to transport and rarely reported to induce epileptic crises, offers a relatively good focality and an excellent temporal resolution and can be used safely when doing it according to established guidelines.

I.IV.1. Transcranial magnetic stimulation (TMS)

Developed in the mid-eighties by Anthony Barker and collaborators, transcranial magnetic stimulation (TMS) is still today the most focal noninvasive brain stimulation technique, largely accepted and used both in fundamental research and clinical applications. Its operating principle is based on Faraday’s law of electromagnetic induction. A stimulating coil is placed on the participant’s scalp. When a short
intense current is discharged through the coil, it generates a brief (0.1-1 ms) and intense (1-4 T) magnetic field perpendicular to the coil surface (Wagner et al. 2007). This pulsed field reaches the brain tissue placed under the coil and induces in it electric currents parallel to the coil surface. The spatial resolution of the technique for a standard 70 mm figure-of-eight coil is about 12 to 14 mm (Valero-Cabre et al. 2005) and the magnitude of the induced current depends on several factors including tissue conductivity, distance between the coil and the targeted brain region and coil design (Valero-Cabre et al. 2005; Wagner et al. 2007).

Different TMS modalities can generate immediate or long-lasting modulations of cortical activity and assess different aspects of brain function. Single TMS pulses, doublets or short bursts yield time-specific immediate “online” effects and are typically employed to probe the causal involvement of a given cortical area in a specific behavioral task and to assess the time window in which the contribution of that area is crucial. The delivery of a single pulse on a trial-by-trial basis at specific time windows over a particular brain area (single-pulse TMS) has been used to causally explore with high temporal resolution the contribution of specific brain regions to human behavior. The highly precise timing at which the pulse can be delivered with regards to specific task events during a trial makes this tool particularly suited to perform the so called chronometric studies. With the aim to disrupt cortical activity during longer but still specific periods of time, doublets or triplets of TMS pulses have been used in online or trial-by-trial TMS designs in many studies (e.g. (Kalla et al. 2008; Koch et al. 2005; O'Shea et al. 2004; Silvanto et al. 2005)).

In contrast, long trains of TMS pulses, known as repetitive TMS (rTMS), yield long-lasting “offline” effects that outlast the duration of stimulation and reflect changes in cortical excitability. Repetitive TMS is typically used to probe the
contribution of different areas to a certain brain process measured through a specific behavioral task without an emphasis on temporal resolution or the potential of the technique to yield long-lasting effects that could be relevant for therapy. The most commonly used patterns are 1 Hz as low frequency and 10 and 20 Hz as higher frequency. Newer patterns of rTMS (e.g. theta burst stimulation, TBS) have combined different frequencies (e.g. 3 pulses at 50 Hz embedded in 5 Hz for TBS) (Huang et al. 2005). Finally, multiple sessions of long trains of stimulation have been shown to yield even longer lasting effects that can be useful for therapeutic purposes.

TMS is known to induce local but also connectivity mediated network effects when used both in the online (Ruff et al. 2006; Ruff et al. 2009) and offline (Valero-Cabre et al. 2007; Valero-Cabre et al. 2005; Wagner et al. 2007) modalities and such network effects appear to depend on the strength of the interactions between areas (Valero-Cabre et al. 2005). Also, its impact has been proven dependent on the ongoing activity levels of the neurons within the stimulated region (Cattaneo et al. 2008; Perini et al. 2012; Silvanto and Muggleton 2008b; Silvanto et al. 2007). Accordingly, paradigms such as neural adaptation (Silvanto et al. 2007) or visuo-spatial cues (Armstrong et al. 2009), which shape the amount of activation of different subpopulations within a given brain area, could be used to shape the effects of TMS (online and offline) and increase its selectivity both in basic research and clinical applications, as well as to further investigate the mechanisms of action of this technique (Silvanto et al. 2008; Silvanto and Muggleton 2008a; Silvanto and Pascual-Leone 2008).

I.IV.2. TMS and the visual system

In the last years, TMS has widely contributed to the causal exploration of the visual
system. Single-pulse TMS over the occipital pole has been shown to yield perceptual modulations. When delivered after the presentation of a visual target, a TMS pulse typically disrupts visual perception (Amassian et al. 1989; Kastner et al. 1998; Maccabee et al. 1991; Miller et al. 1996) although perceptual enhancements have also been reported (Abrahamyan et al. 2011). In contrast, when a single TMS pulse is delivered prior to target onset over occipital regions perceptual enhancements have been described (Mulckhuyse et al. 2011). Perception has also been reported to be enhanced by 1-Hz rTMS over V1 (Waterston and Pack 2010). Moreover, the delivery of a single TMS to higher order visual areas can also modulate visual perception (e.g. for V5, (Amassian et al. 1998; Beckers and Homberg 1992; Beckers and Zeki 1995; Hotson et al. 1994)). TMS has also been used to provide causal evidence for cortico-cortical loops relevant for visual awareness, showing for example that if activity in V1 is modulated using TMS right after V5 activation, visual awareness of motion is disrupted (Pascual-Leone and Walsh 2001). Several studies have used TMS to study the dorsal visual streams in healthy participants. For example, TMS over V5 alters motion perception (Theoret et al. 2002). The use of TMS for the study of the ventral stream has been importantly limited by the inaccessibility of the regions involved (e.g. the fusiform gyrus), and the presence of skeletal muscles, which make the stimulation uncomfortable obliging investigators to work at lower intensities. Nonetheless, stimulation of lateral occipital regions has been shown to affect shape discrimination and distance judgments (Ellison and Cowey 2006) as well as facial recognition (Gilaie-Dotan et al. 2010).

Finally, perceptual modulations can be also yielded by TMS over areas that are not necessarily part of the visual system but involved in processes that are known to be relevant for perceptual performance, such as attention and conscious access
described in prior sections. Two particularly relevant regions for these processes, the FEF and the IPS, and the studies modulating perception from these cortical sites are described in section I.V.

I.IV.3. TMS and brain oscillations

In the last years, brain oscillations have been proven to be extremely important for cognition. As discussed above, neuronal synchronization at different frequency bands could be a general mechanism underlying brain function (Fries 2005). Brain oscillations have been typically studied using methods such as EEG and MEG, able to record brain activity with high temporal resolution. These studies have provided very valuable information on the dynamics of brain activity involved in different cognitive processes. However, causal relationships can be suggested but not established with these techniques.

Single-pulse TMS has been shown to modulate ongoing oscillations and it is likely that it does it through phase resetting (Moliadze et al. 2003). Repetitive TMS has also shown an ability to locally modulate oscillatory activity (Brignani et al. 2008; Fuggetta et al. 2008). Furthermore, the simultaneous stimulation of two cortical sources at a specific TMS frequency can result in lasting enhancements of long-range coupling (Plewnia et al. 2008) as indicated by EEG recordings performed after the stimulation. Although technically challenging, the concurrent use of TMS and EEG (TMS-EEG) has recently provided extremely valuable information on the impact of TMS on brain activity and its potential to manipulate oscillation patterns. The most important limitation of this technique is that each TMS pulse produces an artifact, which can last from hundreds of milliseconds (Thut et al 2003) to 5 ms (Veniero et al. 2009), during which no usable EEG is recorded. Indeed, TMS-EEG requires the
implementation of a system preventing the signal to go into the amplifier when the pulse is delivered to avoid its saturation and the consequent long artifact until the signal recovers. Moreover, a special EEG cap with flat electrodes is also required so that the coil does not stand too far from the scalp and the brain weakening the cortical impact of the stimulation. The combination of TMS and online EEG has provided insights on the relationship between brain oscillations and cortical excitability (Romei et al. 2008; Sauseng et al. 2009; Zarkowski et al. 2006) and shown that single TMS pulses modulate EEG oscillatory activity (Komssi et al. 2002). Moreover, recently, short bursts of TMS have been shown to entrain cerebral oscillations. In particular, it has been reported that TMS bursts at the parietal alpha oscillator preferred frequency entrains local alpha oscillations in a narrow band around it (10-12 Hz), reaching significance after the third of the five pulses of the burst (Thut et al. 2011). Whether the fact that the stimulation is delivered at the preferred frequency of the region plays a key role in the TMS-induced entrainment of oscillations or not remains unclear.

Bursts at different frequencies have been used to noninvasively explore oscillatory phenomena in the human brain and provide causal evidence of their involvement in different cognitive tasks with an acceptable chronometry. For example, occipito-parietal TMS at alpha but not theta or beta control frequencies have been shown to modulate target visibility in a visual detection task (Romei et al. 2010). Similarly, theta and beta TMS over the parietal cortex have been shown to favor processing of global versus local features, respectively (Romei et al. 2011). In spite of their undeniable interest, the comparison of effects across oscillation frequencies in these pioneering studies has been limited by the different duration of the trains. Indeed, trains at higher frequencies are significantly shorter than those
with the same number of pulses at lower frequencies (e.g. 5 pulses at 20 Hz, interstimulus interval of 50 ms, total duration of 200 ms vs. 5 pulses at 10 Hz, interstimulus interval of 100 ms, total duration of 400 ms) and thus one cannot rule out the possibility that different effects result from the different amount of activity induced within a critical time rather than being specific to the frequency used. To the best of our knowledge there is to date a single study that has causally isolated the effect of oscillation frequency on behavior. The investigators of this study, performed in honeybees, pharmacologically induced desynchronization in sensory evidence encoding neurons while keeping unaffected their average firing rate, isolating this way the specific effect of frequency from the level of activation of those neurons. They observed impaired odor discrimination (Stopfer et al. 1997), providing evidence on the role of frequency on behavior.

The use of short TMS bursts to probe the contributions of specific frequencies to behavior in relatively short time windows provides an interesting starting point to causally explore in humans the oscillatory basis of cognition. Furthermore, it opens the door to critically review under new light the results of past online TMS studies in which more than one TMS pulses (typically 2 or 3) were used with the purpose of disrupting activity during longer yet relatively short time windows. Since the pulses in such studies were equally distributed in time, activity was being induced rhythmically, thus if the frequency of the induced activity is proved relevant for behavior the effects could be reinterpreted in terms of oscillations.

Moreover, if local and interregional oscillatory activity proves to be a key element for brain function, pathologies could result from the impairment of these processes. Indeed, altered oscillations have been already associated with several neuropsychiatric diseases including Parkinson’s (e.g. (Brown 2003)), depression (e.g. (Brown 2003)), and...
(Linkenkaer-Hansen et al. 2005)) and schizophrenia (e.g. (Uhlhaas and Singer 2010)). New insights of the specific alterations involved have been revealed by means of the TMS-EEG approaches indicated above (e.g. for schizophrenia see (Farzan et al. 2010; Farzan et al. 2009; Ferrarelli et al. 2008)). This breadth of knowledge will pave the way for a future use of noninvasive neurostimulation to transiently restore normal oscillatory patterns in patients and, if this proved efficient, use such stimulation techniques in longer lasting modality regimes to improve their clinical condition (e.g. for schizophrenia see (Barr et al. 2011)).

I.V. The frontal eye fields, the intraparietal sulcus and their manipulation through noninvasive brain stimulation

Two key regions stand out as involved in the processes relevant for perceptual performance described above, the frontal eye field (FEF) and the intraparietal sulcus (IPS), which have been at the center of our investigations.

The FEF is a cortical area located in the prefrontal cortex of both hemispheres, between the pre-central sulcus and the superior frontal gyrus, and it has been defined according to its role in saccadic activity. Nonetheless, there is controversy with regards to its exact cortical location, which shows some level of interindividual variability and dependence on the mapping technique used (low-current intracortical stimulation studies, fMRI) and the task (sensory guided saccades, antisaccades, memory guided saccades, paradigms with or without a gap between fixation and target onset, lateralized spatial cues as signal for saccades) employed to define it (Amiez et al. 2008; Blanke et al. 2000; Petit et al. 2009; Rasmussen and Penfield 1948).
Some investigators have attempted a causal functional localization of this region as the cortical site in which TMS yields delays in saccade onset, and have reported the FEF to be located 6 cm lateral to the vertex and 0.2 cm posterior to the inter-aural line (Thickbroom et al. 1996) and 1.5 cm anterior to the motor hand area (Olk et al. 2006; Ro et al. 2002). A review of studies using cerebral blood-flow measures obtained with positron emission tomography (PET), localized this region in the vicinity of the precentral sulcus and/or the caudalmost region of the superior frontal sulcus (Paus 1996). More precisely, this study provided averaged Talairach coordinates for the right and the left FEF, which were x=31, y=-2, z=47 and x=-32, y=-2, z=46, respectively. These locations have been successfully employed in TMS studies demonstrating saccadic, attentional and awareness effects (Grosbras and Paus 2002; Grosbras and Paus 2003; Smith et al. 2004).

The frontal eye field is part of a rich brain network of cortical and subcortical sites, sustaining reciprocal connections with other eye field regions (supplementary eye field, parietal eye field), with the intraparietal sulcus (IPS) and the superior temporal sulcus (STS) (Huerta et al. 1987; Stanton et al. 1993; Stanton et al. 1995; Tian and Lynch 1996a; Tian and Lynch 1996b). It also receives afferent connections from the middle superior temporal area (MST) (Tian and Lynch 1996a; Tian and Lynch 1996b) and efferent connections to V2, V3, V4, the occipitotemporal cortex (Stanton et al. 1995), the midbrain (in particular the superior colliculus) and the pons (Leichnetz 1981). The FEF plays a crucial role in the planning and control of eye movements (Rivaud et al. 1994; Schiller et al. 1980). It is also known to contribute significantly in monkeys and humans to the orienting of visuospatial attention, even when eye movements are not involved (i.e. covert attention) (Corbetta et al. 2002; Corbetta et al. 2008) and some recent studies have emphasized a role in the
interaction between attentional orienting and conscious access (Chica et al. 2012). Indeed, electrophysiological recordings in monkeys have shown modulations of neuronal activity in the FEF by attention independently on eye movements (Kodaka et al. 1997) and inactivation of the FEF affects covert attention (Wardak et al. 2006). In humans, TMS studies have provided causal evidence of visuo-spatial attention disruption by modulations of FEF activity during cueing (Grosbras and Paus 2002; Smith et al. 2004) and visual search (Muggleton et al. 2003). Moreover, the FEF has also been shown to modulate activity in visual areas and visual perception. In monkeys, the threshold for detection of a luminance change in an attended target is decreased by microstimulation of FEF neurons coding for the attended location (Moore and Fallah 2001) and this type of interventions enhances responses in striate (V1-V4) and extrastriate (MST, MT) visual and posterior parietal (LIP) areas (Armstrong and Moore 2007; Ekstrom et al. 2008; Ekstrom et al. 2009; Moore and Armstrong 2003). Similarly, using TMS in humans, studies have reported decreases of reaction time (Grosbras and Paus 2002) and awareness enhancements (Grosbras and Paus 2003) in visual detection tasks by pre-target FEF TMS and disruption of discrimination in a visual conjunction search (O’Shea et al. 2004). Used concurrently with fMRI or EEG, FEF TMS has been shown to modulate activity in parietal and visual areas (Capotosto et al. 2009; Ruff et al. 2006) and using occipital TMS evoked phosphenes as a measure of cortical excitability, changes have been reported when FEF was ipsilaterally stimulated 20-30 ms before the visual region (Silvanto et al. 2006). Finally, single TMS pulse in this region has been shown to improve high-beta oscillations around 30 Hz, a likely natural oscillatory activity taking place in this region (Rosanova et al. 2009).
The intraparietal sulcus (IPS) is located in the lateral surface of the posterior parietal cortex (PPC), demarcating the superior and the inferior parietal lobule. Recent TMS studies have used the averaged Talairach coordinates (x=16, y=-63, z=47) provided by a fMRI paper (Kincade et al. 2005) to stimulate the IPS (Bourgeois et al. 2013; Chica et al. 2011).

Its likely homologue in monkeys, the lateral intraparietal area (LIP), has been shown to withhold reciprocal connections with several extrastriate visual regions including V3, V4, MT and MST, as well as with the FEF, the SC and the pulvinar (Andersen et al. 1990; Grieve et al. 2000; Schall et al. 1995). It is involved in spatial representation and visuo-motor processes (Culham and Kanwisher 2001; Grefkes and Fink 2005). Like the FEF, the IPS (or the LIP) plays an important role in visuospatial attention (Corbetta et al. 2002; Corbetta et al. 2008). Moreover, microstimulation of this region has been recently shown to bias saccade direction (Mirpour et al. 2010). Similarly to the FEF, the IPS has been shown to modulate activity and cortical excitability of visual areas (Ruff et al. 2009; Saalmann et al. 2007) and its disruption using TMS alters the occipital phosphene threshold (Silvanto et al. 2009). IPS TMS has also been shown to yield modulations of visual search (Chambers et al. 2004), perception (Bjoertomt et al. 2002; Kanai et al. 2008) and mental rotation (Feredoes and Sachdev 2006).

Finally, some degree of lateralization has been described for cortical networks and processes involving both the FEF and the IPS. For example, although the left and right FEF and the left and right IPS are part of a bilaterally distributed attentional network (Shulman et al. 2010; Thiebaut de Schotten et al. 2011), there is strong evidence of righ-hemisphere dominance for visuo-spatial processes (Bartolomeo et al. 2008; Grosbras and Paus 2002). Similarly, interhemispheric differences have
been reported with regards to prefrontal contributions to conscious access (Del Cul et al. 2009; Rastelli et al.) and perceptual decision-making (Heekeren et al. 2006), with a relevant role of the left hemisphere in such processes.

I.VI. Aims of the present dissertation

Together, the research briefly reviewed in this introduction provides evidence that frontal and parietal areas influence neural activity in the visual cortex and perceptual performance through the different processes in which they are involved. Although the FEF has been shown to be relevant for conscious access of masked stimuli, its causal implication in conscious access of low-contrast unmasked stimuli remains unexplored and conscious access is often associated with the parietal cortex. Moreover, the literature reviewed shows that the temporal dynamics of brain activity is a key element for brain function and that the development of novel procedures and methods to manipulate it can be very useful for exploratory or therapeutic purposes. In particular, available correlational data obtained with fMRI, MEG and EEG needs to be supplemented with causal evidence about the impact of cerebral oscillations in human behavior. In order to contribute to fill this gap, the experiments presented in this dissertation manipulated frontal and parietal activity and provided causal evidence of their relevance for perceptual performance. In particular, we studied how spatiotemporal activity patterns emerging from the FEF and the IPS (known to be involved in several processes such as visuospatial attention and conscious access) may ultimately modulate performance. We focused on visual perception because the visual system constitutes an excellent testing bench thanks to the broad existing wealth of knowledge on its anatomy and function and the possibility to put it to test by means of well-established behavioral paradigms and
measures. We used TMS to induce transient selective non-invasive modulations of neural activity in the human FEF and IPS to provide causal evidence of their role in visual performance, particularly in visual discrimination and conscious visual detection. Importantly, we put special emphasis on the temporal dynamics of neural activity in such regions, by testing the impact of a series of trial-by-trial single pulses or short TMS patterns at specific frequencies and comparing their effects to those yielded by sham TMS, non-frequency-specific active patterns and ‘random’ noise stimulation.

Our overall hypothesis is that fronto-parietal areas contribute to perception through specific spatiotemporal activity patterns, likely to reflect different cognitive processes, and yield selective behavioral contributions to visual performance.

AIM 1: Chapter II: We aimed to explore the causal contribution of frontal pre-target activity to visual discrimination and conscious detection

The modulation of neural FEF activity using single-pulse TMS has been shown to decrease reaction times in response to suprathreshold visual stimuli and to facilitate the detection of masked stimuli. However, causal evidence for the contribution of such area to visual discrimination and conscious detection of low-contrast near-threshold targets remained unclear. Moreover, neuroimaging studies have provided evidence that the orientation of spatial attention using visuo-spatial cues is likely to engage activity within a fronto-parietal network involving the FEF and the IPS. In monkeys, invasive electrophysiological recordings showed that neuronal subpopulations of the FEF coding for attended locations increased their activity and kept them increased during the cue to target period with regards to those units coding for other locations.
In a *first experiment*, single TMS pulses were delivered to the right FEF at different timings prior to the onset of a low-contrast near-threshold target which participants had to subsequently discriminate (line orientation discrimination) and consciously detect. We aimed to causally explore the chronometric contributions of this activity to visual performance. We hypothesized that pre-target FEF activity would be relevant for conscious perception and thus its modulation by means of single TMS pulses would yield perceptual performance modulations. In a *second experiment*, single TMS pulses were delivered after a peripheral predictive visuo-spatial cue engaging attention, likely to modulate FEF activity. An interaction of TMS effects with visuo-spatial attentional orienting, i.e. distinct effect in valid (cue signals target location) and invalid trials (cue does not signal target location) would constitute causal evidence of cue-induced differences in activation of FEF neuronal subpopulations coding for attended vs unattended locations.

**AIM 2: Chapters III, IV and VI:** *We aimed to provide causal evidence of the role played by specific spatiotemporal activity patterns emerging from frontal and parietal areas to visual conscious detection and discrimination*

In a scientific context characterized by growing interest in the oscillatory and synchrony basis of cognition, the specific contribution of oscillatory activity to different aspects of brain function is a topic of major significance and, often, the role for oscillatory phenomena in visual performance and consciousness remains to be explored causally.

In the experiments presented in these three chapters, we delivered 4-pulse TMS bursts at well-controlled interpulse intervals over two cortical regions, the FEF or the IPS, and measured their impact on the discrimination and conscious detection
of low-contrast near-threshold targets. The use of frequency-specific patterns vs. non-frequency-specific ones with equivalent amount of activity induced, i.e. same number of pulses in the same time window at the same stimulation intensity, but slightly differently distributed in time, allowed us to isolate the effects of frequency from those resulting from the activation itself. We hypothesized that the dynamics of frontoparietal activity is a key factor in its ability to contribute to visual performance.

In a **first study (Chapter III)**, we explored the frequency-specific oscillatory basis of visual performance. We delivered real or sham frequency-specific TMS bursts at high-beta (30 Hz) and gamma (50 Hz) frequencies, as well as control non-frequency-specific patterns matched in duration and number of pulses, to the right FEF. We hypothesized that these two frequencies, known to reflect different types of attentional processes, would yield selective effects on visual performance that would not be observed by active non-frequency-specific matched patterns.

In a **second study (Chapter IV)**, we explored potential hemisphere-specific basis of frontal perceptual performance modulations. Real or sham frequency-specific or non-frequency-specific TMS bursts were delivered to the left FEF. We hypothesized that the different involvement of left and right homotopic frontal regions in perceptually relevant processes such as attention and conscious access could yield differences either in the behavioral effects that they yield or in the patterns proving able to do so.

Finally, in a **third study (Chapter VI)**, we assessed the role of high-beta and gamma parietal activity in perceptual performance modulations. Following the same design of the first study we assessed the effects of 30 and 50 Hz in the right IPS on visual performance. We hypothesized that, since the parietal cortex is more directly
and widely connected to visual areas, the effects could be yielded by wider frequency bands or additional effects could be observed.

**AIM 3: Chapter V:** We aimed to causally explore the influence of the phase with regards to target onset of frontal high-beta oscillations on their ability to modulate visual discrimination and conscious detection

Frequency is not the only temporal feature that has been proved to be important for the impact of neural activity on brain function but the phase has also been shown to be extremely relevant. For example, the phase of ongoing oscillations has been shown to predict visual detection and it has been causally linked to cortical excitability. Indeed, the oscillation phase would be defining periods of low and high excitability and thus the time windows in which a perturbation would be more likely to pass a threshold and trigger other processes. Furthermore, single TMS pulses have been shown to induce phase resetting. We used short frequency-specific TMS bursts at 30 Hz on the right FEF to test the behavioral impact of high-beta activity at different oscillation phases, defined as the fraction of cycle between the last TMS pulse of the burst and the visual target onset, on visual performance. We hypothesized that the phase of frontal oscillations could be a relevant factor in the ability of such oscillations to influence performance and thus some phases could be more effective than others in doing so.
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Chapter II
Manipulation of Pre-Target Activity on the Right Frontal Eye Field Enhances Conscious Visual Perception in Humans

Lorena Chanes¹, Ana B. Chica¹,², Romain Quentin¹, Antoni Valero-Cabrè¹,³,⁴*

¹ Groupe de Dynamiques Cérébrales, Plasticité et Rééducation, Équipe Cognition, Neuro-Imagerie et Maladies du Cerveau, CNRS UMR 7225-INSERM UMRS 975-UPMC (Paris VI), Centre de Recherche de l’Institut du Cerveau et la Moelle (CRICM), Paris, France, ² Department of Experimental Psychology, University of Granada, Granada, Spain, ³ Laboratory for Cerebral Dynamics Plasticity and Rehabilitation, Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston University, Boston, Massachusetts, United States of America, ⁴ Cognitive Neuroscience and Information Technology Research Program, Open University of Catalonia (UOC), Barcelona, Spain

Abstract

The right Frontal Eye Field (FEF) is a region of the human brain, which has been consistently involved in visuo-spatial attention and access to consciousness. Nonetheless, the extent of this cortical site’s ability to influence specific aspects of visual performance remains debated. We hereby manipulated pre-target activity on the right FEF and explored its influence on the detection and categorization of low-contrast near-threshold visual stimuli. Our data show that pre-target frontal neurostimulation has the potential when used alone to induce enhancements of conscious visual detection. More interestingly, when FEF stimulation was combined with visuo-spatial cues, improvements remained present only for trials in which the cue correctly predicted the location of the subsequent target. Our data provide evidence for the causal role of the right FEF pre-target activity in the modulation of human conscious vision and reveal the dependence of such neurostimulatory effects on the state of activity set up by cue validity in the dorsal attentional orienting network.

Introduction

Since the pioneering studies by Posner and collaborators [1], the ability of visuo-spatial attentional orienting to influence visual performance has been widely demonstrated. More recent work has specifically reported enhancements in several aspects of visual perception such as spatial resolution, contrast sensitivity and orientation discrimination in those regions of the visual field where attention is willfully focused or involuntarily captured [2,3,4]. Such facilitatory phenomena are thought to be mediated by the ability of long-range connectivity from non-visual regions to reduce background noise, sharpen the tuning, boost the gain, or reduce the variance in firing activity of neuronal populations located within primary visual areas [5,6].

Solid neuroimaging evidence of the human brain has so far helped identify a dorsal network involved in visuo-spatial attentional orienting, with the participation among others, of key cortical sites such as the right Intraparietal Sulcus (IPS) and the Frontal Eye Fields (FEF) [7]. This dorsal system would be supplemented by a ventral network, which would act as a “circuit breaker”, allowing the re-orientation of attention to unexpected and task-relevant events [7,8]. Interestingly, some of these sites appear to co-localize with the nodes of a distributed long-range connectivity network, which, according to theoretical models and neuroimaging data, might play an essential role in access to consciousness [9,10,11,12,13].

Some understanding of FEF interactions with other brain locations has been provided by non-human primate studies revealing that the microstimulation of this area yields selective perceptual modulations for stimuli presented within locations corresponding to the receptive fields of the stimulated neurons, but not outside [14,15]. Likewise, the non-invasive manipulation of the right FEF activity in the human brain by Transcranial Magnetic Stimulation (TMS) has also shown its ability to modulate neural activity in early visual areas [16,17] and visual performance on the detection of high-contrast and masked targets [18,19]. All together those studies suggest that frontal activity has the potential to modulate the processing of visual stimuli, particularly under challenging perceptual conditions. Nonetheless, the processes underlying the ability of this specific cortical frontal site to influence and eventually ameliorate visual perception, particularly when manipulated during the time period preceding the onset of a visual target remain debated.

In the current study, we used single TMS pulses to modulate FEF pre-target activity and studied its impact on the conscious perception of low-contrast near-threshold targets (Experiment 1). Given that neurostimulatory effects have been shown to depend on the pre-existing patterns of activity within the targeted region [20,21], we then made use of visuo-spatial cues, likely to modulate neural activity along the dorsal attentional orienting network, to study whether the effects of pre-target FEF TMS interacted or not.
with the state of activity within that network (Experiment 2). The topic holds the potential to provide novel insights on the role of right FEF activity on conscious visual perception and could also help settle the bases in an upcoming near future, for new strategies to manipulate such region with the goal of enhancing human perceptual capabilities.

Materials and Methods

A group of thirteen participants (8 women and 5 men) aged between 18 and 28 years (average: 24 years old) took part in the study. All participants reported no history of neurological or psychiatric disorders and normal or corrected-to-normal visual acuity. They were all na"ive as to TMS and the purpose of the experiments and participated voluntarily. The research protocol and informed consent was reviewed and sponsored 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 I, Hôpital de la Pitié´-Salpêtrière). Written informed consent was received from all participants in the study prior to participation. Participants took part in two experiments (Experiment 1 and 2), the order of which was counterbalanced across subjects.

Apparatus, Visual Stimuli, and Tasks

Visual stimuli were displayed on an eye tracker screen (Tobii T50, Technology AB, Danderyd, Sweden, 17” wide, 1024×768, 16.67 ms refresh rate) using a laptop computer (Dell Latitude E6400, Round Rock, Texas, USA) and standard stimulus presentation software (E-prime, Sharpsburg PA, USA). All stimuli were presented against a grey background (RGB: 194, 194, 194) (Figure 1) and eye movements were controlled throughout each trial. The fixation point (a black “+” sign of 0.5×0.5”) was displayed in the center of the screen, along with three black squared boxes (6.0” width×5.5” height), one central and two lateral ones (centered 8.5” to the left and right of the fixation point). The target consisted of a Gabor stimulus (2 cycles/deg. spatial frequency, 3.0” diameter, 0.3” of SD, minimum and maximum Michelson contrast of 0.062 and 0.551, respectively), which could appear at the center of one of two lateral boxes for a brief period of time (33 ms). The lines of the Gabors were tilted 1° to 10° to the left or to the right (corresponding 0° to their vertical orientation). Participants were requested to keep fixation on the central cross throughout the trial and to execute two consecutive tasks after the presentation of the target. They were first asked to determine line orientation (categorization task), as fast and as accurately as possible, by pressing the corresponding button on a computer keyboard with the index and middle finger of their right hand (“1” for left and “2” for right). In this task, we encouraged them to respond to every trial within a window of 2000 ms, and to guess a response when the target was not presented or they did not consciously perceive it. Performance was assessed through accuracy and reaction time measures. Secondly, participants were required to report whether they had consciously seen the target or not (detection task). To do so, two arrow-like stimuli, one below and one above the fixation cross (>>> and <<<), pointing to the left and to the right side of the screen were presented. Participants were provided with three keys, which they had to operate with their left hand: an upper key (“d”), a lower key (“c”) and the space bar. The upper key signaled the side of the screen pointed by the arrow presented in the upper part of the fixation point, while the lower key was associated to the side of the screen pointed by the lower arrow. Participants had to respond by pressing the space bar if they did not see the stimulus, or, if they did see it, with the corresponding key (“d” or “c”) to indicate the location where the target had been consciously perceived (left or right). The position of the arrows pointing left or right was randomized across trials. Perceptual sensitivity (d’) and response bias (beta) used in Signal Detection Theory [22,23] served to assess performance in this task. The former (d’) is a bias-free statistic that provides a measure of observers’ ability to detect weak signals, while the latter (beta) describes their relative preference for one response over the other. To compute these two 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”; and finally, trials in which the location of a present target was incorrectly reported by participants (4% of the ‘seen’ targets in both experiments) were excluded from the analyses as errors.

A titration procedure performed prior to the experimental trials allowed to determine, in each experiment and for each participant, the stimulus contrast at which ~62% of the displayed targets were consciously reported in the detection task and the degree of line tilting for which performance in the categorization task remained between 65 and 85% correct. Participants started the titration trials with a high contrast stimulus and, every 20 trials, target contrast and line tilting were adjusted in order to converge to the above-mentioned criteria. Experimental trials started once such performance levels were attained and during the experiment, this whole set of stimulus parameters was also automatically adjusted every 20 trials to avoid behavioral fluctuations caused by task practice or fatigue.

In Experiment 1, every trial started with a fixation screen lasting randomly from 1000 to 1500 ms in order to achieve an inter-trial interval of at least two seconds. The fixation cross became then slightly bigger (0.7×0.7”) for 66 ms to signal the upcoming event. After an Inter Stimulus Interval (ISI) of 233 ms, the target could appear at the center of one of the two lateral boxes. The experiment consisted of 600 trials, including 120 trials in which the target was absent. In half of the trials, chosen randomly, a single TMS pulse was delivered on the right FEF either at 80, 100 or 140 ms prior to the target onset (active TMS trials). In the other half (sham TMS trials), a single pulse was delivered, at those same timings, 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.

In Experiment 2, everything was kept the same as in Experiment 1 except for the following. The fixation sign did not increase its size but, instead, a visuo-spatial cue, consisting of a black circle (1.5” diameter), was presented in the upper external corner of one of the two lateral boxes and displayed for 66 ms. After the same ISI (233 ms), the target could appear at the center of the cued (valid trial) or uncued (invalid trial) lateral box. The cue was predictive about the location of the upcoming target (75% valid and 25% invalid trials). A cue was considered valid when it correctly signaled the location of the upcoming target (left or right), and invalid when it incorrectly signals target location. A valid trial was the one including a valid cue whereas the opposite applied to invalid trials. Similarly, validly cued targets were those preceded by a valid cue, whereas invalidly cued targets were preceded by an invalid cue. The experiment consisted of 800 trials, including 160 target-absent trials. Active or sham TMS pulses were only delivered 80 ms pre-target onset, given the inability to test all three timings and keep the session within a reasonable duration. Prior experiments suggested that short pre-target timings had the highest potential to induce behavioral effects [19].
Transcranial Magnetic Stimulation (TMS)

TMS pulses were delivered using a biphasic repetitive stimulator (Superapid, Magstim, Withland, UK) with a 70 mm diameter figure-eight air-cooled coil (Figure 2). Pulses were triggered through E-prime software (E-prime, Sharpsburg PA, USA) running on a laptop computer (Dell, Latitude 6410). Prior to the experimental tasks, a structural T1-weighted MRI scan was acquired for every participant at the CENIR MRI center (Hopital de la Pitie-Salpetriere, Paris). A 3T Siemens MPRAGE sequence, flipangle = 9, Repetition Time = 2300 ms, Echo Time = 4.18 ms, slice thickness = 1 mm, was used. For the TMS experiments, the right FEF region was localized using previously identified Talairach coordinates \(x = 31, y = -2, z = 47\) [24] and labeled with a 0.5 cm radius spherical Region of Interest (ROI) in the MNI space with the Marsbars toolbox (Sourceforge.net). Using SPM5 software (UCL, London, UK), each participant’s structural MRI image was segmented into white and gray matter and the inverse segmentation matrix was used to individually de-normalize the ROI (spatial smooth isotropic Gaussian Kernel of 1-mm full-width half-maximum). The same software was used to co-register the de-normalized ROI with each participant structural MRI volume, obtaining a precise individual localization of the area. The final MRI was uploaded into a frameless stereotaxic system (eXimia NBS System, Nexstim, Helsinki, Finland) and reconstructed in 3D for online neuronavigation of the TMS coil. Given the small size of the region and the high inter-individual variability in FEF location, a TMS-guided individual functional confirmation of the location of the right FEF was conducted by following a well-established protocol based on evidence that a single TMS pulse delivered on the FEF during the preparation time of a saccade has the ability to delay its onset [25].

At all times, the active TMS coil was held tangential to the skull, with its handle oriented \(45^\circ\) in a rostral-to-caudal and lateral-to-medial orientation, i.e., parallel to the central sulcus. The TMS coil was kept steady within an area of \(2 \text{ mm}\) radius from the targeted region by using online neuronavigation feedback on each participant’s structural MRI. For all interventions, stimulation intensity was initially set up for every subject at 67% of the TMS machine maximum output. Nonetheless, in some participants, intensity had to be slightly decreased to abolish temporal involuntary muscle activation, involuntary blinks or other types of facial sensations. The average intensity at which participants were stimulated was 66 ± 1% for both experiments (113 ± 12% and 111 ± 15% of the mean resting motor threshold in Experiments 1 and 2, respectively).

Data Analysis

Trials in which participants showed response anticipations, i.e. pressed the button before stimulus presentation (0.02% and 0.01% of all trials respectively), or broke fixation and performed eye movements to one of the lateral boxes (3% and 6% of all trials for Experiment 1 and 2, respectively) were eliminated from the analyses. The first three participants taking part in Experiment 1...
could not be included in the analyses due to a software programming error.

As accuracy in the categorization task was high when participants correctly reported to have seen the target (74% in both experiments) and remained at chance levels when they reported not to have seen it (51% and 49% in Experiment 1 and 2, respectively), only correctly seen target trials were considered for reaction time and accuracy analyses. For each timing (80, 100 and 140 ms), TMS condition (active or sham TMS) and validity (valid and invalid), trials with reaction time faster than 150 ms and outside 4 standard deviations of the mean (0.1% and 0.4% in Experiment 1 and 2, respectively) were eliminated from the analyses as outliers.

All behavioral outcomes (accuracy and reaction time for the categorization task and perceptual sensitivity and response bias for the detection task) were subjected to a repeated measures ANOVA with timing (80, 100 and 140 ms), target location (left and right) and TMS condition (active and sham TMS) as within-participant factors in Experiment 1 and with validity (valid and invalid), target location and TMS condition as within-participant factors in Experiment 2. Such analysis was also performed for detection errors (i.e. target-present trials in which participants incorrectly indicated target location) to rule out any potential TMS effects on these specific types of events. In Experiment 1, no significant main effects or interactions were observed in such trials. In Experiment 2, only a main effect of validity was observed, indicating that participants made fewer errors in valid than invalid trials (F(1, 12) = 13.64, p = 0.003).

**Results**

In Experiment 1, we used single TMS pulses on the right FEF to test the ability of pre-target activity on this region to modulate conscious visual perception of low-contrast near-threshold targets. Participants correctly reported to have seen the target in 56% of the present-target trials and the mean rate of false alarms was 2%. All measures (accuracy and reaction time for the categorization task and perceptual sensitivity and response bias for the detection task) were subjected to a repeated measures ANOVA with timing (80, 100 and 140 ms), target location (left and right) and TMS condition (active and sham TMS) as within-participant factors. In the categorization task, no significant effects of TMS condition were observed. Only a main effect of target location in reaction time reached significance (F(1, 9) = 7.88, p = 0.020), participants being faster for targets displayed on the right than on the left visual hemifield. Responses also proved to be more accurate when responding to right than left targets (F(1, 9) = 6.68, p = 0.030).

In contrast, in the detection task, a main effect of TMS condition
reached significance, with overall higher perceptual sensitivity (d') under active than sham TMS pulses (F(1,9) = 8.31, p = 0.018). On the basis of the a priori hypothesis that stimulation should depend on pulse delivery time, we performed three separate repeated measures ANOVA for the three TMS timings, with side and TMS condition as within-participant factors. The TMS effect only reached significance when pulses were delivered 80 ms pre-target onset (F(1, 9) = 9.77, p = 0.012), but not when applied 100 ms (F = 5.09, p = 0.031) or 140 ms (F = 3.95, p = 0.078) pre-target onset (Figure 3 and Table 1). No main effects or interactions reached statistical significance for the response bias (beta).

In Experiment 2, FEF TMS was delivered after the engagement of the dorsal attentional orienting network by a peripheral visuo-spatial cue, which was predictive about the location of the subsequent target. Given our purpose of studying the combined effects of a single TMS pulse and a cue-driven engagement of attentional orienting, only participants effectively orienting their attention according to the cue, and thus exhibiting cueing effects under sham TMS trials, were considered for further analyses. An assessment of the perceptual effects induced by visuo-spatial attentional orienting using the exact same paradigm (see Experiment 4 in [26] for details) demonstrated that, for this very same categorization task, effective visuo-spatial attentional orienting entailed significant reaction time reductions in valid as compared to invalidly cued targets. Accordingly, the presence of a significant cueing effect was statistically assessed in our participants by comparing the mean reaction time of valid vs. invalid sham TMS trials. Seven out of the thirteen participants showed statistically significant reductions of reaction time for valid vs. invalid sham TMS trials (unpaired 1 tailed t-test, p<0.05) and thus were considered as exhibiting cueing effects.

Those participants reported to have seen the target in 58% of the present-target trials and the mean rate of false alarms was 6%. All measures (accuracy and reaction time for the categorization task and perceptual sensitivity (d') and response bias (beta) for the detection task) were subjected to a repeated measures ANOVA with validity (valid and invalid), target location (left and right) and TMS condition (active and sham TMS) as within-participant factors. In the categorization task, only a main effect of validity in reaction time reached significance (F(1, 6) = 60.22, p<0.001), with faster responses for valid than invalid trials. In the detection task, a significant interaction between validity and TMS condition was observed on perceptual sensitivity (F(1, 6) = 6.54, p = 0.043), indicating the dependency of TMS effects on the validity of the cue. More specifically, active stimulation improved perceptual sensitivity (d') only when the cue correctly predicted the location of the target (valid trials), as compared to sham TMS (F = 19.26, p = 0.005). Interestingly, no differences between active and sham TMS were observed for invalid trials, in which the cue incorrectly predicted the location of the target (F<1) (Figure 4, Table 2). No
significant main effects or interactions were observed for the response bias (beta).

Discussion

The potential of non-invasive brain neurostimulation to boost cognitive performance beyond the limits set up by individual skills and capabilities in healthy [27,28,29,30,31,32,33] and pathological states [34,35,36,37,38] has been postulated for more than a decade. Thanks to its ability to activate discrete cortical regions and associated networks [39], TMS, a focal magnetically-based non-invasive brain stimulation technique, has been shown to induce punctual or lasting changes in the firing patterns of restricted key cortical regions and, in virtue of such capabilities, influence normal or pathological human behavior [40,41]. We hereby assayed in healthy humans whether conscious visual perception can be modulated by focal pre-target TMS paradigms.

Table 1. Data from TMS-induced modulations of right FEF pre-target activity on visual performance (Experiment 1).

<table>
<thead>
<tr>
<th>Task</th>
<th>Mean values ± SE</th>
<th>TMS condition</th>
<th>80 ms</th>
<th>100 ms</th>
<th>140 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LVF</td>
<td>RVF</td>
<td>LVF</td>
</tr>
<tr>
<td>Detection</td>
<td>d’ score</td>
<td>Sham</td>
<td>1.82 ± 0.16</td>
<td>2.03 ± 0.13</td>
<td>1.79 ± 0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active</td>
<td>2.05 ± 0.15</td>
<td>2.20 ± 0.09</td>
<td>2.03 ± 0.13</td>
</tr>
<tr>
<td>Beta measure</td>
<td></td>
<td>Sham</td>
<td>5.69 ± 0.45</td>
<td>5.66 ± 0.29</td>
<td>4.66 ± 0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active</td>
<td>5.60 ± 0.37</td>
<td>6.84 ± 0.34</td>
<td>5.91 ± 0.33</td>
</tr>
<tr>
<td>Categorization</td>
<td>RT (ms)</td>
<td>Sham</td>
<td>849 ± 55</td>
<td>778 ± 51</td>
<td>805 ± 38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active</td>
<td>840 ± 52</td>
<td>792 ± 53</td>
<td>833 ± 52</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td>Sham</td>
<td>0.68 ± 0.03</td>
<td>0.79 ± 0.04</td>
<td>0.70 ± 0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active</td>
<td>0.77 ± 0.02</td>
<td>0.79 ± 0.02</td>
<td>0.69 ± 0.03</td>
</tr>
</tbody>
</table>

Perceptual sensitivity (d’ scores, mean ± SE) and response criterion (beta measures, mean ± SE), and reaction time (RT) (mean ± SE) and accuracy (mean ± SE), for the three different TMS delivery timings (80, 100 and 140 ms pre-target onset), obtained respectively for the conscious visual detection and visual categorization tasks explored in Experiment 1. Data are presented for targets displayed in the visual field contralateral (left visual field, LVF) and ipsilateral (right visual field, RVF) with respect to the stimulated right FEF under the effects of active or sham TMS pulses.

doi:10.1371/journal.pone.0036232.t001

Perceptual sensitivity (d’ scores, mean ± SE) and response criterion (beta measures, mean ± SE), and reaction time (RT) (mean ± SE) and accuracy (mean ± SE), for the three different TMS delivery timings (80, 100 and 140 ms pre-target onset), obtained respectively for the conscious visual detection and visual categorization tasks explored in Experiment 1. Data are presented for targets displayed in the visual field contralateral (left visual field, LVF) and ipsilateral (right visual field, RVF) with respect to the stimulated right FEF under the effects of active or sham TMS pulses.

doi:10.1371/journal.pone.0036232.t001

Figure 4. TMS-induced modulations of FEF pre-target activity on conscious detection after cue-driven attentional orienting (Experiment 2). Perceptual sensitivity (mean ± SE) for targets displayed in the visual field contralateral (left visual field, LVF) or ipsilateral (right visual field, RVF) with respect to the stimulated right FEF site under active TMS (red) or sham TMS (blue). An interaction between validity and TMS proved statistically significant (F(1, 6) = 6.54, p = 0.043) indicating that, when delivered after the presentation of a peripheral predictive visuo-spatial cue, TMS pulses yielded significant bilateral enhancements of conscious visual detection only when the cue correctly signaled the location of the subsequent target (valid trials, F = 19.26, p = 0.005, indicated by the asterisk), whereas no effects were observed when the cue incorrectly predicted it (invalid trials, F < 1).

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perception of low-contrast near-threshold targets could be enhanced with non-invasive neurostimulation, by modulating the activity of the right FEF prior to the onset of a visual target. Such brain region has been shown to be involved in visuo-spatial attentional orienting [7] and also to have bearing on conscious access [9,10,11,12,13] for visual stimuli. In agreement with prior work [14,15,18,19,42], our data from Experiment 1 indicate that right FEF pre-target activity is indeed relevant for conscious perception and that its non-invasive manipulation with TMS can induce relevant visual perceptual sensitivity improvements. Interestingly, when the dorsal attentional orienting network was previously activated by means of peripheral predictive visuo-spatial cues (Experiment 2), the modulation of right FEF pre-target activity with TMS pulses brought visual perceptual sensitivity modulations, which were shaped according to cue validity. More specifically, only when the prior visuo-spatial cue correctly predicted the site (left or right) of the subsequent target (valid trials) but not when it incorrectly predicted it (invalid trials), TMS induced facilitatory effects on conscious detection. These results suggest that cue-driven neural activations related to attentional orienting interact with conscious perception and have the potential to sculpt the effects of time locked pre-target FEF stimulation and render such perceptual facilitatory outcomes more specific. In spite of the lack of an active control condition mimicking not only the TMS clicking noise but also the scalp tapping sensations, the lack of significant effects when TMS pulses were combined with invalid spatial cues became an internal control that rules out a hypothetical contribution of such phenomena to our results.

Prior studies have demonstrated that the impact of non-invasive neurostimulation can be highly influenced by the pre-existing patterns of activity within the stimulated region and its associated networks [20,21]. In our experiments, visuo-spatial cues could have differentially modulated the firing patterns of distinct neuronal subpopulations within the right FEF region, prior to the onset of neurostimulation, and hence have primed the effects of FEF TMS only for those under certain states of activation. In support of this hypothesis, non-human primate research has shown that peripheral predictive visuo-spatial cues increase (and maintain increased along the cue-to-target period) the firing patterns of the FEF neurons that specifically code for the signaled location, but not for those whose receptive fields lay outside the cued site [43]. On the basis of this observation, different activity levels or ‘states’ of activation across FEF neuronal subpopulations as driven by visuo-spatial cues could easily explain how, on a trial-by-trial basis, highly selective visual facilitation patterns could emerge from the stimulation of roughly the same cortical resources as a function of cue validity [44].

Our data indicate that the FEF TMS visual facilitatory effects interacted with the orienting of spatial attention engaged by means of predictive spatial cues. Nonetheless, given the frequently hypothesized role of the right FEF not only as a crucial node of the dorsal attentional network but also as relevant in providing access to consciousness, which of these two systems might have been ultimately responsible for the observed visual facilitatory effects remains unclear. Contributing to the discussion of this issue, our data reveal that FEF TMS neither when used in isolation (Experiment 1) nor when combined with visuo-spatial cues (Experiment 2) did modulate the reaction times or accuracy levels for the visual categorization task. A behavioral study performed and published separately by our group assessed the behavioral effects of visuo-spatial attentional orienting in the same exact paradigm, and showed significant shorter reaction times in response to stimuli presented at attended than unattended locations (see [26] Experiment 4 for details). The latter effects, which were accompanied by a modulation in perceptual sensitivity in the detection task only when the cue was predictive about target location, strongly suggest that cue-validity effects in such paradigm should be considered a solid signature of attentional orienting. On such basis, it is tempting to interpret the current lack of reaction time modulations for the categorization task, accompanying improvements in visual detection by FEF pre-target activity modulations, not as ultimately mediated by the manipulation of visuo-spatial orienting processes but reflecting a genuine effect of right FEF TMS on visual consciousness. In spite of obvious differences between intact and damaged systems, this interpretation could be in agreement with patient work showing a relevant role of the prefrontal cortex in access to consciousness of masked stimuli, not accountable either by attentional orienting processes [45]. Nonetheless, given that attention can alter appearance [3] and that in our paradigm composed of two serial tasks, subjects could have eventually sacrificed reaction time for accuracy, or categorization performance for detection performance, whether attention can modulate conscious visibility without affecting reaction time remains an open question.
Our data contribute further evidence in support of the notion that the right FEF and its associated systems may constitute according to monkey [14,15,42] and human [19,44] data, a key area facilitating access to consciousness for visual stimuli. Moreover, our combined modulation strategy based on an ‘at will’ stimulation of the FEF and the presentation of visuo-spatial cues, showed its ability to selectively enhance human visual awareness for low-contrast near-threshold stimuli and to shape the specificity of such effects, thus setting up the stage for the use of TMS on the direct manipulation of visual conscious perception in healthy and pathalogical states. Unfortunately, in absence of brain neuroimaging data, we cannot yet rule out if such facilitatory phenomena were driven locally at the stimulated right FEF and directly manipulated by the alleged ability of this area to contribute to visual awareness; emerged from connectivity-conveyed trans-synaptic effects on primary visual regions through fronto-parietal-occipital top-down projections [17,46]; or resulted from the modulation of other intermediate cortical or subcortical structures interconnected with the FEF. This remains a highly relevant question to be addressed in an immediate future through specific experiments which, as elegantly performed elsewhere [17,46] might require the combination of stimulation and neuroimaging. Moreover, in the current study, we manipulated activity patterns within the right FEF since this area is a key component of the dorsal network devoted to visuo-spatial attentional orienting; its anatomical location can be individually confirmed through a well-established mapping procedure; there is precedence on its ability to induce connectivity mediated functional modulation on visual regions, and in consideration of its hypothesized role in visual awareness. In agreement with findings suggesting the dominant role of the right hemisphere sites in attentional orienting and consciousness [18,19,27], our intervention in the right FEF proved similarly efficacious for right and left targets. Prior studies have also reported bilateral effects for right FEF activity modulations, whereas the manipulation of the left FEF stimulation would be restricted to an influence on targets presented in the right visual hemifield. Future venues will have to explore the role of left FEF pre-target activity in conscious visual perception and the extent of such effects throughout the visual field. Furthermore, functional MRI and TMS brain-function studies suggest that the modulation of non-necessarily frontal regions, such as the right intraparietal sulcus or the angular gyrus [7] could potentially also interact with cue validity and result in visual facilitatory effects, and thus they would also deserve to be explored in similar paradigms in the future.

In sum, our findings show that FEF pre-target activity can be effectively manipulated to influence conscious visual perception using non-invasive neurostimulation methods, and that a combined strategy based on right hemisphere frontal stimulation and visual cues can be implemented not only to episodically enhance visual performance, but to shape the selectivity of those effects. The fact that a combination of TMS and attentional cues can indeed improve visual sensitivity should be considered a proof of concept that visual capabilities can be manipulated and improved through those approaches. On that basis, strategies operating on cerebral sites involved in attentional orienting and conscious access could become a reality to punctually increase visual capabilities in healthy participants. Similar principles could be also applied to clinical rehabilitation, aiming at containing visual acuity losses in patients with retinal defects, and allowing the emergence of episodic or lasting periods of conscious vision in cortically damaged patients. Nonetheless, it should also be strongly emphasized that the ameliorations demonstrated in our study operate trial-by-trial and remain extremely short lasting. Furthermore they have been demonstrated for lateralized right or left peripheral detections and thus might not equally occur for targets presented in other locations of the visual hemifield. Both aspects weaken the current applicability of the results for meaningful behavioral ameliorations in healthy individuals or therapeutic applications in patients. In order to overcome such limitations, however, longer rTMS patterns and multi-day rTMS regimes combined with spatial cuing paradigms remain to be studied and evaluated for their ability to generate lasting increases in visual sensitivity. Similarly, the differential ability of TMS based approaches to generate ameliorations for targets presented at different visual field locations than those tested in the current paper would need to be studied before our findings could be considered potentially interesting for clinical applications.

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Author Contributions
Conceived and designed the experiments: LC ABC AVC. Performed the experiments: LC ABC AVC. Analyzed the data: LC ABC RQ AVC. Contributed reagents/materials/analysis tools: LC ABC AVC. Wrote the paper: LC AVC. RQ Contributed to data analysis and manuscript discussions leading to the written interpretations included in this PLoS ONE submission: RQ.

References
Brief Communications

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

Lorena Chanes,1 Romain Quentin,1 Catherine Tallon-Baudry,1,2 and Antoni Valero-Cabré1,3,4

1Université Pierre et Marie Curie, CNRS UMR 7225–INSERM UMRS 5975, Groupe Centre de Recherche de l’Institut du Cerveau et la Moelle (ICM), 75013 Paris, France, 2Laboratoire de Neurosciences Cognitives, INSERM-ENS UMR960, 75005 Paris, France, 3Laboratory for Cerebral Dynamics Plasticity and Rehabilitation, Boston University School of Medicine, Boston, Massachusetts 02118, and 4Cognitive Neuroscience and Information Technology Research Program, Open University of Catalonia (UOC), 08035 Barcelona, Spain

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’), whereas gamma frequency shifted 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-
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/m², 2500 ms), followed by a fixation screen (randomly lasting between 1000 and 1500 ms) (Fig. 1a). The fixation cross (0.5° × 0.5°) was displayed in the center, along with three rectangular boxes (6.0° × 5.5°): 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° × 0.7°, 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° 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 (< < or > >) 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 ~50% of the displayed targets were correctly 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 line of sight. 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 stimulus 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 MRPRAGE, 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 $x = 31, y = -2,$
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.

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.

At all times, the TMS coil was held tangentially to the skull, with its handle oriented ~45° 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 ~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 ± 13% and 74 ± 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 × 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
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 ± 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
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. 2a, left). Moreover, no significant main effects or interactions were observed for the response criterion (Fig. 2b, 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. 2a, right). However, the uniform pattern shifted response criterion \( (\text{significant interaction between block and TMS condition, } F_{(1,13)} = 6.42, p = 0.025) \). 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. 2b, 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 how 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 exceedingly 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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Chapter IV
Stochastic facilitation by left frontal arrhythmic activity patterns reveals hemisphere-specific coding strategies for conscious visual perception

Lorena Chanes¹, Romain Quentin¹, Marine Vernet¹, Antoni Valero-Cabrè¹,²,³*

¹ Université Pierre et Marie Curie, CNRS UMR 7225-INSERM UMRS S975, Centre de Recherche de l’Institut du Cerveau et la Moelle (ICM), 75013 Paris, France.
² Laboratory for Cerebral Dynamics Plasticity & Rehabilitation, Boston University School of Medicine, Boston, MA 02118, USA.
³ Cognitive Neuroscience and Information Technology Research Program, Open University of Catalonia (UOC), 08035 Barcelona, Spain.

Corresponding author (*): Dr. Antoni Valero Cabré, MD PhD, CNRS-INSERM-Université Pierre et Marie Curie. ICM, Equipe Cognition, Neuro-imagerie et maladies du Cerveau; Groupe de Dynamiques Cérébrales, Plasticité et Rééducation. Hôpital de la Salpêtrière, 47-boulevard de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: avalerocabre@gmail.com; avalero@bu.edu
Summary

The frontal eye field (FEF) is a brain region involved in several processes relevant for visual performance, including visuo-spatial attention, access to consciousness and decision-making. Prior research has casually demonstrated that frontal high-beta FEF activity in the right hemisphere enhances conscious visual perception, an outcome that is in agreement with evidence of beta synchronization along a right dorsal fronto-parietal network during attentional orienting and with a right-hemisphere’s dominance in spatial attention. However, frontal regions in the left hemisphere have also been shown to contribute to the modulation of perceptual performance. To causally explore the neural basis of these contributions, we delivered high-beta \textit{frequency-specific} activity to the left FEF and report that in this region, these patterns failed to modulate conscious perception. In contrast, both \textit{rhythmic} and \textit{random} \textit{arrhythmic} \textit{non-frequency-specific} activity patterns yielded visual performance improvements similar to those formerly reported by high-beta activity on its right-hemisphere homotopic area. Our study yields support for stochastic facilitation of conscious vision by \textit{non-frequency-specific} activity on the left frontal cortex, and suggests a behaviorally relevant role for the induction of neural noise in the modulation of visual perception. Furthermore, taken together with prior causal right FEF evidence, our results indicate that frontal regions in both hemispheres contribute to the modulation of conscious visual perception through different neural coding strategies.

Keywords

Perceptual Facilitation, Rhythmic Transcranial Magnetic Stimulation, Plasticity, Cognition.
Introduction

Research developed in the last decades is unveiling an intriguing link between brain activity, temporal dynamics and human cognition. Specific frequency bands on particular brain regions and their associated networks have been correlated to distinct cognitive processes. Interestingly however, differences or similarities in the modulation of behavioral correlates by characteristic spatiotemporal patterns in homotopic brain areas of opposite hemispheres have rarely been addressed.

In the current study, we focused on the frontal eye field (FEF), a cerebral region contributing in humans to the planning of saccadic activity, visuo-spatial attention, conscious access and decision-making (Chanes et al. 2012; Corbetta et al. 2008; Libedinsky and Livingstone 2011; Moore and Armstrong 2003; Paus 1996). The right and left FEF are part of a bilaterally distributed dorsal attentional orienting network (Shulman et al. 2010; Thiebaut de Schotten et al. 2011). Prior research has provided strong evidence of right hemisphere dominance for visuo-spatial attentional processing (Bartolomeo et al. 2008; Grosbras and Paus 2002). Similarly, interhemispheric differences have been reported with regards to prefrontal contributions to visual consciousness (Del Cul et al. 2009; Rastelli et al.) or decision-making (Heekeren et al. 2006), suggesting a relevant role for the left hemisphere in these processes.

Here, we explored the impact of high-beta frequency-specific as compared to rhythmic and random arrhythmic non-frequency-specific activity, delivered to the left FEF in short bursts of transcranial magnetic stimulation (TMS). The effects observed are compared to those formerly recorded in its right homotopic region, which consisted in increases of perceptual sensitivity on a conscious visual detection task with high-beta frequency-specific (but not rhythmic non-frequency-specific) activity
patterns (Chanes et al. 2013), likely to reflect attentional orienting-related processes (Buschman and Miller 2007; Phillips and Takeda 2009).

Similar results on the left FEF would indicate similar coding strategies of the left and right frontal cortex to modulate perceptual performance. In contrast, the observation of facilitatory effects by non-frequency-specific activity would provide causal evidence in support of a different coding strategy for perceptual modulation. In particular, performance enhancements by random arrhythmic patterns would reflect stochastic facilitation and support a behaviorally relevant role for noise activity in neural coding (McDonnell and Ward 2011; Medina et al. 2012).

Materials and methods

Participants and consent

Twelve participants (7 women and 5 men) aged between 20 and 31 years old (24±4) took part in the first experiment (left FEF frequency-specific and rhythmic non-frequency-specific patterns). Eleven of them were naïve as to TMS and to the purpose of the experiment. A new group of 12 participants (6 women and 6 men, 4 of them having participated in the first experiment) aged between 21 and 39 (25±5) took part in the second experiment (left FEF random arrhythmic non-frequency-specific patterns). All subjects participated voluntarily and reported no history of neurological or psychiatric disorders and normal or corrected-to-normal vision. 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). The apparatus, visual stimuli and TMS stimulation procedure employed here on the left FEF were identical to those reported for the right FEF in a recent publication (Chanes et al. 2013).
Chapter IV - Figure 1. Experimental design. (a) A low-contrast near-threshold target consisting in a Gabor could be briefly displayed within a left or a right placeholder. Participants were requested to perform a forced-choice visual discrimination task (Gabor lines orientation: clockwise/counterclockwise), followed by a conscious visual detection task (did you see the target and, if yes, where: left/right placeholder). (b) Schematic representation of the temporal distribution of the 4 pulses of the TMS burst in frequency-specific, rhythmic non-frequency-specific and random arrhythmic non-frequency-specific patterns. (c) Example of a sagittal, axial and coronal brain sections and TMS coil positioning on the left FEF displayed in a 3D-reconstructed native MRI.

Visual stimuli were displayed on an eye-tracker screen (Tobii Technology AB 17” wide, 1024x768) using a laptop computer (Dell Latitude E6400) and standard stimulus presentation software (E-prime). Each trial started with a grey resting screen (luminance: 75 cd/m2, 2500 ms), followed by a fixation screen (randomly lasting between 1000 and 1500 ms) (Chapter IV - Figure 1a). The fixation cross (0.5x0.5°) was displayed in the center, along with three black rectangular placeholders (6.0°x5.5°): 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 (0.7x0.7°, 67 ms) to alert participants of an upcoming event. After an inter-stimulus interval (233 ms), a target could appear at the center of one of the two lateral placeholders 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, minimum and maximum Michelson contrast of 0.037 and 0.283, respectively) with its lines tilted 1° to 10° clockwise or counterclockwise from the vertical orientation. The inter-trial interval lasted at least 4 seconds.

Participants were asked to execute two tasks. First, they had to determine the orientation of the Gabor lines (discrimination task) by pressing the corresponding button on a computer keyboard (“1” for counterclockwise and “2” for clockwise) with the index and middle fingers of their right hand. Participants were forced to guess a response even when the target was not presented or they did not consciously perceive it and accuracy was collected as the outcome measure. Secondly, they had 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 arrow 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 given key (“d” or “c”) to select the upper or lower arrow pointing to the placeholder (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. Perceptual sensitivity is a bias-free measure that informs on the participants’ ability to detect weak signals in situations that might be strongly influenced by belief whereas response criterion describes the relative preference of participants for one response over the alternative one, independently on signal strength. To compute these measures, trials in which the location of a target was correctly determined by participants were considered as correct detections or “hits” and trials in which participants reported a location for targets that were not presented were considered “false alarms”. Trials in which the location of a present target was incorrectly reported were counted as “errors”. Eye movements were monitored for fixation control purposes. Fixation was considered broken when participants’ eyes position was recorded outside the central placeholder (i.e. 3° away from the fixation cross horizontally and 2.75° vertically).

A titration procedure performed prior to the onset of the experiment, allowed us to determine for each participant the stimulus contrast at which ~50% of the displayed targets were consciously reported. The degree of line tilting was also adjusted individually to maintain discrimination performance at ~75% of correctly reported targets. Such titration levels ensured that, in both tasks, performance was halfway between the worse (0% in the detection task and 50% in the forced-choice discrimination task) and the best possible performance (100% in both tasks). Participants started the titration trials with a high contrast stimulus and, every 20 trials, target contrast and line tilting were adjusted in order to converge to the pre-established criteria. The experiment started once performance levels reached those criteria. Throughout the experiment, stimulus parameters were automatically adjusted every 20 trials (in steps of 0.07 Michelson contrast and 1° of tilting) to maintain these titration levels.
Each participant performed two experimental blocks, each of them consisting 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 delivered on the left FEF (active TMS trials). In the other half (sham TMS trials), the same short burst was applied by a second TMS coil placed next to the stimulation site, with the coil’s surface perpendicular to the scalp, preventing the magnetic field from reaching the skull and stimulating the brain. The order of active and sham TMS bursts was randomized across trials in sub-blocks of 20 trials. Participants were allowed to take a short break and received feedback on the screen about performance and eye movement rates every 40 trials.

In the first experiment, each participant performed two blocks of trials the order of which was counterbalanced across subjects. In the frequency-specific 30 Hz block, the 4 TMS pulses were uniformly delivered across a 102 ms time interval, whereas, in the rhythmic non-frequency-specific block, these were unequally distributed over the same time window (the first and last pulses occurred at identical timing as in the frequency-specific block, whereas the second and third pulses were slightly anticipated and delayed respectively, Chapter IV - Figure 1b). After the titration and before the two experimental blocks, participants performed a few short blocks of familiarization in which they performed the task with the stimulation.

The second experiment consisted in a single block, in which random arrhythmic patterns of TMS were employed. In those patterns, the temporal distribution of the TMS pulses changed across trials, so that the first and last of the 4 pulses were delivered at the same timing as in the first experiment, whereas the second and third pulses were delivered randomly during the interval left by the former two, but subjected to the following constraints: (i) the 2 middle pulses were delivered at least 19 ms apart, in order to ensure consistent TMS capacitor recharge time; and
(ii) the 4 pulses of the burst could not be equally distributed across the burst interval, in order to avoid occurrence of the frequency-specific pattern employed in Experiment 1.

**Transcranial Magnetic Stimulation (TMS)**

TMS pulses were delivered using a biphasic repetitive stimulator (SuperRapid) with a 70 mm diameter figure-of-eight coil. A structural T1-weighted MRI scan (3T Siemens MPRAGE, flip angle=9, TR=2300 ms, TE=4.18 ms, slice thickness=1mm) was acquired for every participant at the CENIR MRI center (Salpêtrière Hospital, Paris). The left FEF region was localized on each individual MRI using averaged Talairach coordinates x=31, y=-2, z=47 (Paus 1996) and a 0.5 cm radius spherical Region of Interest (ROI). 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, Nextim) (Chapter IV - Figure 1c).

At all times, the TMS coil was held tangentially to the skull, with its handle oriented ~45° in a rostral-to-caudal and lateral-to-medial orientation, i.e. ~parallel to the central sulcus. Coil position was tracked online throughout the experiments and kept steady within an area of ~1-2 mm radius from the targeted site. The representation of the right and left primary motor cortices (M1) of the abductor pollicis brevis (APB) muscle were localized and the motor thresholds at these sites were determined as the TMS intensity yielding thumb twitching responses in ~50% of the attempts. In the first experiment, stimulation intensity was set up at 45% of the TMS machine maximal output. Nonetheless, in one participant such level had to be slightly decreased to abolish temporal involuntary facial muscle activation, blinks and other types of facial sensations induced by field spread. The average intensity at which participants were stimulated was 44.8% (SD: 0.6%), which corresponded to 70% of
the mean individual motor threshold. In the second experiment, stimulation intensity was also set up at 45% of the TMS machine maximal output, a value that corresponded to 71% of the mean individual motor threshold.

**Data analyses**

In the first experiment, trials in which participants broke fixation (7±10%) were eliminated from the analyses. Moreover, trials in which participants reported to have seen the target but incorrectly determined its location (errors, 3±3% of reported targets) were also excluded. In the detection task, the mean perceptual sensitivity was 1.8 (SD: 0.2) and the mean response criterion was 5.0 (SD: 0.7). In the discrimination task, one participant was excluded from the analyses because he did not perform the task correctly (his mean accuracy along the experiment was under chance levels). Participants' general accuracy (mean±SD) was 63±6%. It was high when they reported to have seen the target (74±8%), and it remained at chance levels when they reported not to have seen it (51±6%). Only correctly detected target trials were considered for accuracy analyses. Each outcome measure (perceptual sensitivity and response criterion for the conscious detection task and accuracy for the discrimination task) was subjected to a 2x2x2 repeated measures ANOVA with block (frequency- and rhythmic non-frequency-specific), target location (left and right visual fields) and TMS condition (active and sham) as within-participant factors. The same ANOVA was performed on the excluded error trials. This analysis did not yield any significant main effects or interactions indicating that the percentage of errors was similarly distributed across conditions.

Similarly, trials of the second experiment in which participants broke fixation (7±10%) or incorrectly determined the location of seen targets (errors, 5±5%) were eliminated. In the detection task, mean perceptual sensitivity was 1.8 (SD: 0.3) and
the mean response criterion was 4.8 (SD: 0.8). Participants’ general accuracy in the discrimination task (mean±SD) was 63±4%. Again, it was high when subjects reported to have seen the target (76±7%), and it remained at chance levels when they reported not to have seen it (50±5%). Each outcome measure was subjected to a 2x2 repeated measures ANOVA with target location (left and right visual fields) and TMS condition (active and sham) as within-participant factors. The same ANOVA was performed on the eliminated error trials. A main effect of TMS (F(1,11)=6.667, p=0.026) was observed, indicating that participants made more errors under the impact of active than sham TMS bursts.

Results

Our first experiment revealed pattern-specific modulatory effects of frontal activity on visual performance (Chapter IV - Figure 2). In the conscious detection task, an interaction between block and TMS condition reached statistical significance for perceptual sensitivity (repeated measures ANOVA with block, target location and TMS condition as within-participant factors, F(1,11)=5.34, p=0.041), indicating different effects of TMS in each of the stimulation blocks. Whereas no differences were observed between active and sham stimulation for frequency-specific 30-Hz bursts (planned comparison active vs. sham TMS: F<1), perceptual sensitivity proved higher for active than sham TMS in the rhythmic non-frequency-specific block (planned comparison active vs. sham TMS: F=5.95, p=0.033). Given that, as previously reported for this region, perceptual effects could differ across the visual field and be rather contralateral with respect to the stimulation site (Grosbras and Paus 2002), we performed additional separate planned comparisons for left and right targets of the rhythmic non-frequency-specific block. Significant effects were
observed for contralateral (planned comparison active vs. sham TMS for the right visual field: F=11.78, p=0.006) but not ipsilateral (planned comparison active vs. sham TMS for the left visual field: F<1) targets. In addition to the significant interaction block x TMS condition, a main effect of target location reached significance (F(1,11)=23.16, p=0.001), indicating that participants performed better for right than left targets. No significant main effects or interactions were observed for response criterion in the detection task or for accuracy in the discrimination task.

In order to confirm that the effect of rhythmic non-frequency-specific bursts on conscious visual detection resulted from the lack of frequency-specificity of the TMS patterns employed and not from the specific temporal features embedded in it, we performed a second experiment in which random arrhythmic non-frequency-specific bursts (i.e. noise activity) were employed. In the conscious detection task, the interaction between target location and TMS condition reached statistical significance for perceptual sensitivity (repeated measures ANOVA with target location and TMS condition as within-participant factors, F(1,11)=16.96, p=0.002), indicating that active random arrhythmic patterns improved performance as compared to sham for targets contralateral (planned comparison active vs. sham TMS for the right visual field: F=8.91, p=0.012) but not ipsilateral (planned comparison active vs. sham TMS for the left visual field: F=2.35, p=0.154) to the TMS coil location. In addition, a main effect of target location reached significance (F(1,11)=8.39, p=0.015), indicating better performance for right than left targets. As in the first experiment, no significant main effects or interactions were observed for response criterion (beta) in the detection task or for accuracy in the discrimination task.


Chapter IV - Figure 2. Effects of frequency-specific, rhythmic non-frequency-specific and random arrhythmic non-frequency-specific TMS bursts on perceptual sensitivity. Bars represent perceptual sensitivity (d') for targets displayed in the ipsilateral (left, L) and contralateral (right, R) visual fields (VF) with regards to the stimulated site. Asterisks (*) indicate statistically significant differences (p<0.05) between active and sham TMS. (a) Frequency-specific 30 Hz TMS bursts did not yield significant effects on visual sensitivity as compared to sham TMS. In contrast, both rhythmic and (b) random arrhythmic non-frequency-specific patterns enhanced perceptual sensitivity.

The equivalence of the results for the rhythmic non-frequency-specific block employed in the first experiment and the random arrhythmic non-frequency-specific block tested in the second experiment was further tested by performing a 2x2 repeated measures ANOVA with TMS condition (active or sham) and target location (right or left fields) as within-participant factors and group (rhythmic and random arrhythmic non-frequency-specific) as between-participant factor. As expected, an interaction between target location and TMS condition was observed, indicating an effect of TMS only for contralateral (right) but not ipsilateral (left) visual targets. No interactions with group were observed, indicating that both rhythmic and random arrhythmic non-frequency-specific patterns yielded similar results.

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Discussion

We here explored the impact of left frontal activity patterns on the discrimination and conscious detection of low-contrast near-threshold targets. Interestingly, the identical design of the current work with regards to a prior right-FEF study (Chanes et al. 2013) allows for direct comparison of the results across hemispheres.

For both hemispheres, none of the stimulation patterns used impacted accuracy in the forced-choice visual discrimination or response criterion in the conscious detection task. On the contrary, different hemisphere-specific patterns of stimulation enhanced perceptual sensitivity. Whereas high-beta frequency-specific activity on the right FEF enhanced perceptual sensitivity in the conscious visual detection task (Chanes et al. 2013), on the left frontal homotopic area, this same activity pattern failed to yield any significant impact on visual performance in the exact same behavioral task. In contrast, both rhythmic and random arrhythmic non-frequency-specific blocks significantly enhanced conscious visual performance. This perceptual facilitation by the injection of neural noise to a frontal brain region constitutes experimental evidence of behavioral stochastic facilitation (McDonnell and Ward 2011; Medina et al. 2012).

Taken together, the results for the left and right FEF suggest that both hemispheres contribute to visual performance through different coding strategies, which could underlie the same or different cognitive processes. Previously reported effects for the right FEF (Chanes et al. 2013) were in agreement with a dominant role for the right hemisphere in visuo-spatial attentional orienting processes (Bartolomeo et al. 2008; Grosbras and Paus 2002) and frequency-specific beta synchronization.
along the right fronto-parietal dorsal attentional orienting network (Buschman and Miller 2007; Phillips and Takeda 2009). As for the right FEF (Chanes et al. 2013), left FEF effects on conscious visual detection may have emerged from the modulation of visuo-spatial processes. For example, attentional synchronization along the right dorsal fronto-patietal network could have benefited through transcallosal interactions from the induction of noise to the left hemisphere. Another possibility is that the perceptual effects observed did not resulted from attentional processes but rather from the modulation of other (non-attentional) cognitive processes also relevant for visual performance, such as or decision-making or access to visual consciousness to which the left FEF is known to contribute to (Del Cul et al. 2009; Heekeren et al. 2006; Rastelli et al. 2013). For example, target omission in visuo-spatial neglect patients has been associated with left prefrontal beta-band synchronization (Rastelli et al. 2013), and, in line with this observation, the induction of noise activity to the left frontal cortex could have prevented the build-up of such rhythms and facilitated detection. Whether this injection of noise is enhancing or suppressing ongoing neural activity in one or more frequency bands remains elusive in the absence of accompanying electrophysiological recordings. A challenging combination of frequency-specific and non-frequency-specific non-invasive stimulation patterns and online EEG recordings will be necessary to understand the specific mechanisms by which noise induction results into the observed facilitation of visual performance.

In sum, our study provides support for stochastic visual facilitation through the induction of non-frequency-specific activity to the left frontal cortex, and shows that right and left homotopic human frontal regions induce similar behavioral effects on conscious visual perception through different coding strategies (beta synchronization vs. stochastic facilitation). Future research will explore the functional links between
right and left frontal contributions to perceptual performance and will further characterize the specific cognitive processes that these underlie, among those involving the FEF and their associated networks.

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Chapter V
Causal contributions of induced frontal beta oscillation phase to the modulation of visual performance in humans

Lorena Chanes¹, Romain Quentin¹, Marine Vernet¹, Antoni Valero-Cabré¹.².³*

¹ Université Pierre et Marie Curie, CNRS UMR 7225-INSERM UMRS S975, Centre de Recherche de l’Institut du Cerveau et la Moelle (ICM), 75013 Paris, France.
² Laboratory for Cerebral Dynamics Plasticity & Rehabilitation, Boston University School of Medicine, Boston, MA 02118, USA.
³ Cognitive Neuroscience and Information Technology Research Program, Open University of Catalonia (UOC), 08035 Barcelona, Spain.

Corresponding author (*): Dr. Antoni Valero-Cabré, MD PhD, CNRS-INSERM-Université Pierre et Marie Curie. ICM, Equipe Cognition, Neuro-imagerie et maladies du Cerveau; Groupe de Dynamiques Cérébrales, Plasticité et Rééducation. Hôpital de la Salpêtrière, 47-boulevard de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: avalerocabre@gmail.com; avalero@bu.edu
Summary

High-beta oscillatory activity in the right frontal eye field has been causally related to improvements of conscious visual perception of near-threshold targets. Nonetheless, the role of the oscillation phase with regards to target onset remains unexplored. We here assessed the impact of high-beta activity induced by transcranial magnetic stimulation delivered at several pre-target onset phases on visual discrimination and conscious detection performance. Our results confirmed prior perceptual sensitivity enhancements induced by 30 Hz bursts on conscious detection and show that these effects are phase-independent. Unexpectedly, the phase of high-beta activity influenced response criterion, what has been previously reported to result from the induction of frontal gamma activity. We hypothesize that this outcome may reflect phase-to-power interactions between frontal beta and gamma activity. Together, our data gather support for phase-independent perceptual enhancements by high-beta activity patterns and potential local cross-frequency effects of rhythmic noninvasive stimulation on the right human frontal eye field, which could be possibly employed to manipulate and improve cognition in investigational and clinical applications.

Keywords

Introduction

Recent studies on the impact of frontal, parietal and occipital activity on perceptual performance have provided causal evidence that spatiotemporal activity patterns induced by transcranial magnetic stimulation (TMS) have the ability to modulate visual perception in a frequency-specific manner (Chanes et al. 2013; Romei et al. 2011; Romei et al. 2010).

Although prior research efforts have concentrated in the role of oscillation frequency, the phase is also known to be a key factor in neural activity function. In the domain of perception, studies have reported that the phase of ongoing alpha oscillations predicts visual detection (Busch et al. 2009; Jaegle and Ro 2013) and this same parameter has been proven to be causally linked to cortical excitability in occipital sites (Dugue et al. 2011). Moreover, the phase of lower frequency oscillations, particularly in the theta-band, has been found to modulate the power of higher frequency oscillations, such as those in the gamma-band (Canolty et al. 2006; Jensen and Colgin 2007; Lakatos et al. 2008; Mormann et al. 2005). Recent work has also revealed that increases of alpha oscillatory activity on occipito-parietal locations by 5-pulse TMS bursts is enhanced mainly beyond the third pulse of each pattern and that such entrainment effects tend to dissipate extremely quickly, in a matter of a cycle and a half at those frequencies (Thut et al. 2011).

We here focused on the frontal eye field (FEF), a cerebral region contributing in humans to the planning of saccadic activity, visuo-spatial attention, conscious access and decision-making (Chanes et al. 2012; Corbetta et al. 2008; Libedinsky and Livingstone 2011; Moore and Armstrong 2003; Paus 1996). The right and left FEF are part of a bilaterally distributed dorsal attentional orienting network (Shulman et al. 2010; Thiebaut de Schotten et al. 2011) although there is strong evidence of
right hemisphere dominance for visuo-spatial processing (Bartolomeo et al. 2008; Grosbras and Paus 2002). In a prior study, we showed that right FEF high-beta and gamma activity had a different impact on visual performance. In particular, high-beta but not gamma activity proved able to selectively enhance perceptual sensitivity in a conscious detection task leaving response criterion unchanged, whereas gamma activity shifted response criterion without changes in perceptual sensitivity (Chanes et al. 2013).

Using an identical behavioral paradigm and high-beta 4-pulse TMS bursts, we explored whether the phase of the induced right frontal pattern with regards to target onset was able to modulate the effect of such in the conscious detection of a low-contrast near-threshold stimulus. In accordance with prior literature in other frequency bands (Busch et al. 2009; Dugue et al. 2011; Jaegle and Ro 2013), we hypothesized that the phase of TMS-induced high-beta activity pattern would influence its ability to impact perceptual outcomes, and such phase-dependent visual performance facilitatory effects would become weaker as the last pulse of the stimulation patterns is moved temporally further from target onset.

Materials and methods

Fourteen right-handed participants (10 women and 4 men) aged between 18 and 25 years old (21±2) took part in the study. All of them were naïve as to TMS and to the purpose of the experiment. They all participated voluntarily and reported no history of neurological or psychiatric disorders and normal or corrected-to-normal vision. 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).
Apparatus, stimuli and procedure

Visual stimuli were displayed on a screen (22") using MATLAB and the Psychtoolbox running in a personal computer (HP Z800). Each trial started with a grey resting screen (luminance: 31 cd/m2, 2500 ms), followed by a fixation screen (randomly lasting between 1000 and 1500 ms) (Chapter V - Figure 1a). The fixation cross (0.5x0.5°) was displayed in the center, along with two laterally located rectangular placeholders (6.0°x5.5°) centered 8.5° to the left and to the right of the fixation point. Then, the fixation cross became slightly larger (0.7x0.7°, 67 ms) to alert participants of an upcoming event. After an inter-stimulus interval (233 ms), a target appeared or not at the center of one of the placeholders for a brief period of time (33 ms). The target consisted of a low-contrast Gabor stimulus (0.5 degree/cycle sinusoidal spatial frequency, 0.6 degree exponential standard deviation, minimum and maximum Michelson contrast of 0.005 and 1, respectively) with its lines tilted 1° to 10° clockwise or counterclockwise from the vertical orientation. The inter-trial interval lasted at least 4 seconds.

Participants were asked to execute two tasks. First, they had to determine the orientation of the Gabor lines (discrimination task) by pressing the corresponding button on a computer keyboard (“1” for counterclockwise and “2” for clockwise) with the index and middle fingers of their right hand. They were forced to guess a response even when the target was not presented or they did not consciously perceive it and accuracy was collected as the outcome measure. Secondly, they had to report whether they consciously perceived the target or not and, if they did, where (conscious detection task). To do so, two arrow-like signs (“>>>” 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 arrow 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 given key (“d” or “c”) to select the upper or lower arrow pointing to the placeholder (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 in situations in which signals are presented around the threshold of perception and responses might be strongly influenced by belief. Perceptual sensitivity is a bias-free measure that informs on the participants’ ability to detect an item. Response criterion describes the relative preference (bias) of participants for one response over the alternative one (i.e. a preference for ‘yes I perceived the target’ over ‘no, I did not perceive the target’ or viceversa), independently on signal strength. To compute these measures, trials in which the location of a target was correctly determined by participants were considered as correct detections or “hits” and trials in which participants reported a location for targets that were not presented were considered “false alarms”. Trials in which the location of a present target was incorrectly reported were counted as “errors”. Eye movements were monitored for fixation control purposes (Eyelink 1000, SR Research). Fixation was considered broken when participants’ eyes position was recorded outside a circle of 2° around the fixation cross anytime from 300 ms before target onset to the end of target presentation. If this occurred, participants received an alert message the trial was randomized with the rest of the trials left in the block and repeated.
A titration procedure performed prior to the onset of the experiment, allowed us to estimate for each participant the stimulus contrast at which ~50% of the displayed targets were consciously reported and the degree of line tilting for which the discrimination performance was ~75% of correctly reported targets. Such titration levels ensured that, in both tasks, performance was halfway between the worse (0% in the detection task and 50% in the forced-choice discrimination task) and the best possible one (100% for both tasks). Participants started the titration trials with a high initial stimulus contrast and a high initial tilting angle. A one-up/one-down titration staircase procedure was used to determine the threshold level (50% correct responses in the conscious detection task), with an initial contrast step equal to the initial contrast, then divided by two at each change of direction of the staircase procedure but kept always larger than 0.005 Michelson contrast. We considered that the threshold had been steadily reached when the last five consecutively tested contrasts were not different by more than 0.01 Michelson contrast. In parallel, the degree of line tilting was titrated using a one-up/three-down titration staircase procedure to determine the threshold level (75% of correct response in the discrimination task), with an initial angle step equal to the initial angle, then divided by two at each change of direction of the staircase procedure but kept always an integer and larger than 1°. We considered that the threshold had been steadily reached when, the contrast being already set, the last five consecutively tested angles were not different by more than 2° of tilting.

Once the two titrations were completed, participants performed between 1 and 4 blocks of familiarization during which right FEF-TMS patterns were employed. Each of these blocks consisted of 20 trials, including 4 trials in which the target was absent. In half of the trials, a short burst of 4 TMS pulses was delivered on the right FEF
(active TMS trials). In the other half (sham TMS trials), the same short burst was delivered by a second TMS coil placed next to the real stimulation site, with the coil’s surface perpendicular to the scalp, preventing the magnetic field from reaching the skull and stimulating the brain. The order of active and sham TMS bursts was randomized across trials. At the end of each familiarization block, if performance in sham TMS trials fell outside titration levels, stimulus parameters were adjusted in steps of 0.05 Michelson contrast and 1° of tilting. Experimental trials started only once steady levels of performance in both visual tasks, discrimination and conscious detection, were reached. Nonetheless, throughout the experiment, stimulus parameters were also automatically adjusted in steps of 0.005 Michelson contrast and 1° of tilting every 20 trials according to performance levels in sham TMS trials to maintain titration levels (45-55% for the detection task and 65-85% for the discrimination task). As in the familiarization blocks, within each of these 20 trials sub-blocks, half of the trials used active TMS and the other half sham stimulation. Participants were allowed to take a short break and received feedback on the screen about their percentage of “false alarms” and “errors”.

We explored the effects of frequency-specific high-beta (30 Hz) activity patterns on visual performance. All participants performed 5 experimental blocks, corresponding to the 5 phases/conditions tested, the order of which was randomized across subjects (Chapter V - Figure 1b). Each one consisted of 140 trials (including 28 trials in which the target was absent) and corresponded to a specific phase determined by the time elapsed between the last pulse of the TMS burst and the target onset. The shortest phase corresponded to \( \pi \), i.e. half a cycle (time lag of \( \sim 17 \) ms between the last pulse and target onset), whereas the longest one was \( 3\pi \), i.e. one and a half cycle (time lag of 50 ms). In between those values, we tested phases
for every quarter of the 30 Hz cycle. In summary, the 5 tested phases were: \( \pi \), \( 3\pi/2 \), \( 2\pi \), \( 5\pi/2 \) and \( 3\pi \), i.e. \( 2/4 \), \( 3/4 \), \( 4/4 \), \( 5/4 \) and \( 6/4 \) of cycle corresponding to a time lag of ~17, 25, ~33, ~42 and 50 ms, respectively, between the last TMS pulse and the target onset.
Chapter V - Figure 1. Experimental design. (a) A low-contrast near-threshold target (Gabor stimulus) could be briefly displayed within a left or a right placeholder. Participants were asked to perform a forced-choice discrimination task (lines orientated clockwise/counter-clockwise), followed by a conscious detection task (‘did you see the target or not’ and, if yes, in which the left or the right placeholder). (b) Schematic representation of the temporal distribution of the four pulses of the TMS burst in the five conditions tested (five phases), which corresponded to different time elapsed between the last pulse and target onset. (c) Sagittal, axial and coronal brain sections and TMS coil positioning on the right FEF displayed in an individual MRI and corresponding 3D-reconstruction by the neuronavigation system.

Transcranial Magnetic Stimulation (TMS)

TMS pulses were delivered using a biphasic repetitive stimulator (Magstim SuperRapid) with a 70 mm diameter figure-of-eight coil. A structural T1-weighted MRI scan (3T Siemens MPRAGE, flip angle=9, TR=2300 ms, TE=4.18 ms, slice thickness=1mm) was acquired for every participant at the CENIR MRI center (Pitié-Salpêtrière Hospital, Paris). The right FEF region was localized on each individual MRI using averaged Talairach coordinates x=31, y=-2, z=47 (Paus 1996) and a 0.5 cm radius spherical Region of Interest (ROI). This same coordinates have been successfully employed in preceding experiments in our lab (Chanes et al. 2012; Chanes et al. 2013). The final MRI was uploaded into a frameless stereotaxic system and reconstructed in 3D for its use in an online stereotaxic TMS neuronavigation system (Brainsight, Rogue Research Inc.) (Chapter V - Figure 1c). At all times, the TMS coil was held tangentially to the skull, with its handle oriented ~45° in a rostral-to-caudal and lateral-to-medial orientation, i.e. ~parallel to the central sulcus.

The position of the active coil was tracked online throughout the experiments and kept steady within an area of ~1-2 mm radius from the targeted site. For population characterization purposes we determined on each participant the right
hemisphere’s motor resting threshold. This was measured on the cortical hotspot of the *abductor pollicis brevis* (APB) muscle in the right primary motor cortex (M1) and defined as the TMS intensity yielding thumb responses in ~50% of the attempts. Stimulation intensity was set up at a fixed value of 45% of the TMS machine maximal output as used previously (Chanes et al. 2013) and we verified that no observable temporal involuntary facial muscle activation, blinks and other types of facial sensations were induced by field spread. The intensity used corresponded to 72% of the mean individual motor thresholds.

**Data analyses**

Each outcome measure (perceptual sensitivity and response criterion for the conscious *detection* task and accuracy for the *discrimination* task) was subjected to a 5x2x2 repeated measures ANOVA with block (each of the 5 phases, i.e. π, 3π/2, 2π, 5π/2, 3π), target location (left and right visual field) and TMS condition (active and sham) as within-participant factors. The same analysis was performed for errors (3% of reported targets) and did not yield any significant main effects or interactions, indicating that percentage of errors was similar across conditions.

**Results**

In the detection task, the mean perceptual sensitivity (d’) was 1.8 (SD: 0.3). The repeated measures ANOVA revealed a main effect of TMS (F(1,13)=13.56, p=0.003), with higher perceptual sensitivity levels for active than sham stimulation. With the a priori hypothesis that some burst-to-target phases should work better than others, we tested the comparison between active and sham TMS for each specific block/phase. The TMS effect reached significance for all phases except for the one in which the last pulse of the burst was most distanced from target onset (i.e., 50 ms,
$3\pi$) ($F=8.47$, $p=0.012$; $3\pi/2$: $F=7.66$, $p=0.01$; $2\pi$: $F=5.72$, $p=0.033$; $5\pi/2$: $F=12.81$, $p=0.003$; $3\pi$: $F=1.60$, $p=0.228$), indicating that enhancement of perceptual sensitivity by high-beta frontal activity is phase independent and rather limited to a time window close to target onset (Chapter V - Figure 2).

Chapter V - Figure 2. Effects of high-beta TMS bursts at different phases on perceptual sensitivity in the conscious visual detection task. Bars represent perceptual sensitivity for targets displayed in the ipsilateral (left, L) and contralateral (right, R) visual fields (VF) with regards to the stimulated site. Asterisks (*) indicate statistically significant differences ($p<0.05$) between active and sham TMS and for $0.05<p<0.10$ the exact value is indicated. High-beta (30-Hz TMS) stimulation improved perceptual sensitivity in a phase-independent manner, particularly when the burst was delivered closer to the target.

The mean response criterion (beta) accounted by the group was 4.1 (SD: 0.9). A repeated measures ANOVA revealed a main effect of TMS ($F(1,13)=8.35$, $p=0.013$) on this parameter, with less conservative response criterion for active than sham TMS bursts. Again, with the a priori hypothesis that the effects could differ
across phases, we tested the comparison between active and sham TMS for each phase/block. Interestingly, the TMS effect was either not far from significance or significant for alternate phases: \( \pi \) (\( F=3.49, p=0.084 \)), \( 2\pi \) (\( F=5.78, p=0.032 \)) and \( 3\pi \) (\( F=7.07, p=0.020 \)) as opposed to phase \( 3\pi/2 \) (\( F=1.07, p=0.321 \)) and \( 5\pi/2 \) (\( F<1 \)), for which criterion was not modulated (Chapter V - Figure 3).

Chapter V - Figure 3. Effects of high-beta TMS bursts at different phases on response criterion in the conscious visual detection task. Bars represent response criterion for targets displayed in the ipsilateral (left, L) and contralateral (right, R) visual fields (VF) with regards to the stimulated site. Asterisks (*) indicate statistically significant differences (\( p<0.05 \)) between active and sham TMS and for \( 0.05<p<0.10 \) the exact value is indicated. High-beta (30-Hz TMS) stimulation shifted response criterion in a phase-dependent manner, particularly when the burst was delivered further from the target.

In the discrimination task, participants’ general accuracy was 64±7% (mean±SD). As expected, it was high when they reported to have seen the target (75±10%), and it remained at chance levels when they reported not to have seen it
When only responses to correctly-detected target were considered for accuracy analyses, no main effects or interactions were observed, indicating that conscious discrimination was not significantly affected by high-beta right FEF patterns at any of the phases tested in the study. However, when discrimination responses were independently considered from conscious access (both correctly detected and undetected trials were taken into account), a main effect of TMS was observed ($F(1,13)=32.42$, $p<0.001$), indicating that participants discriminated more accurately with active than sham TMS patterns. When the same output measure was tested separately for the different phases, the comparison between active and sham TMS reached significance only for phase $5\pi/2$ ($F=18.67$, $p<0.001$), whereas phase $3\pi/2$ and $2\pi$ were marginally significant ($F=3.99$, $p=0.067$ and $F=4.66$, $p=0.050$, respectively) and the earliest and latest phases ($\pi$ and $3\pi$) did not yield significant effects ($F=3.30$, $p=0.092$ and $F=2.37$, $p=0.148$, respectively) (Chapter V - Figure 4).

Chapter V - Figure 4. Effects of high-beta TMS bursts at different phases on the forced-choice visual discrimination task. Bars represent accuracy for targets displayed in the ipsilateral (left, L) and
contralateral (right, R) visual fields (VF) with regards to the stimulated site. Asterisks (*) indicate statistically significant differences (p<0.05) between active and sham TMS and for 0.05<p<0.10 the exact value is indicated. 30-Hz TMS bursts improved accuracy when they were delivered in a specific time window.

Discussion

We here tested the effect of the phase, defined by the time elapsed between the last pulse of a high-beta pattern and target onset, on previously proven facilitatory effects on conscious visual detection. Our results are in agreement with prior findings (Chanes et al. 2013) showing a causal relation between high-beta activity induced in the right FEF and improvements of perceptual sensitivity (d') during the conscious detection of near-threshold targets. Most importantly, they also demonstrate that such high-beta (30 Hz) frontal modulation, which had been previously probed for TMS bursts delivered 1/2 of an oscillation cycle (i.e. ~17 ms, π phase) prior to target onset, appears to be phase-independent, and thus that similar effects can be induced when the last pulse of the rhythmic TMS pattern is delivered at up to 5/4 of a cycle (i.e., ~42 ms, 5π/2) from target onset, but not at the longest interval used here (i.e. 50 ms, 3π). As shown elsewhere for occipito-parietal alpha induced oscillations, these data prove that the behavioral effects associated to right frontal high-beta spatio-temporal patterns operate on a very restricted time scale, and exert an influence during the stimulation pattern and only shortly beyond their duration (Thut et al. 2011).

Our data also show that response criterion (beta), a signal detection measure characterizing the relative preference for one response over the other one independently on signal strength, appears to be modulated by the phase of high-beta frontal activity with regards to target onset. In particular, only oscillation patterns that
were in phase or in opposition of phase (i.e. 2π, 3π), but not at intermediate phases (i.e. 3π/2 and 5π/2), and rather further away from the target (the results for π did not reach statistical significance) proved able to induce significant shifts of response criterion. In line with these observations, in a previous study (Chanes et al. 2013), no significant effect on participants’ response criterion was observed for high-beta patterns, identical to the ones used here with a π phase. On the contrary, in that same study, 50 Hz bursts significantly shifted response criterion (they made it less strict), demonstrating a causal role of gamma activity in the modulation of criterion. Taken together, these results suggest that a possible explanation for the high-beta effects on response criterion could be through cross-frequency interactions (Jensen and Colgin 2007). Indeed, the phase of lower frequency oscillations, particularly in the theta-band, has been found to modulate the power of higher frequency oscillations, such as those in the gamma-band (Canolty et al. 2006; Jensen and Colgin 2007; Lakatos et al. 2008; Mormann et al. 2005). We hypothesize that, through a similar mechanism, the phase of our high-beta oscillations could have modulated higher-frequency neural activity and yielded effects associated with gamma band. If this hypothesis happened to be true, the influence of high-beta over gamma frequency patterns could take a bit of time to set up and so the effect would difficulty reach significance if high-beta activity is induced too close to target onset (e.g. in the case of phase π in this study). A demonstration of this hypothesis would require concurrent electrophysiological recordings, for example a TMS-EEG design, so that the time-frequency signature of high-beta patterns on the stimulated region during and immediately following the end of the pulses can be assessed. Successful EEG recordings showing oscillation entrainment have been achieved for alpha-band stimulation patterns (Thut et al. 2011) but those remain technically complex and
extremely challenging at higher frequencies of stimulation such as those in the beta or the gamma band, with very limited periods of inter-pulse artifact-free data to analyze.

Our study also revealed unexpected improvements of visual discrimination accuracy, which TMS either in single pulses or identical high-beta patterns with a π phase failed to impact in prior studies when applied to this very same right cortical area (Chanes et al. 2012; Chanes et al. 2013). Such effect only arose when all trials, and not only those in which the target was correctly consciously detected, were considered in the analyses. This indicates that high-beta frontal activity patterns can affect performance at a perceptual level further than specifically impacting conscious access. Very interestingly, this effect did not reach significance for the earliest nor the latest tested phase value (π and 3π, i.e. ~17 and 50 ms), separated by one oscillation cycle. This observation could reflect either that such effect on visual discrimination is phase-independent but only arises if right-FEF activity is engaged within a short critical time window, or that it is phase-dependent and fails to reach significance when high-beta activity is induced in phase opposition to target onset (π and 3π). Further studies will be needed to understand in detail the mechanisms underlying such phenomenon.

In sum, our study provides causal evidence for a timing-dependent impact of high-beta right frontal oscillatory activity on visual discrimination, which could be assayed in novel TMS-based visual rehabilitation applications to boost their efficiency. These same patterns also proved able to induce phase-independent improvements of conscious visual detection reflected by perceptual sensitivity enhancements, and response criterion shifts that appeared to depend on the pattern phase with regards to target onset. Future research with concurrent TMS-EEG
recordings will contribute to elucidate if the phase-dependent effects on criterion reported here are genuine or yielded through cross-frequency interactions between high-beta and higher (gamma) activity patterns at right frontal brain locations.

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Chapter VI
Distinct causal contributions of frequency and non-frequency-specific posterior parietal activity patterns to visual performance

Lorena Chanes¹, Romain Quentin¹, Seth Elkin-Frankston², Dimitri Bayle¹, Marine Vernet¹, Antoni Valero-Cabrè¹,²,³*

¹ Université Pierre et Marie Curie, CNRS UMR 7225-INSERM UMR S975, Centre de Recherche de l’Institut du Cerveau et la Moelle (ICM), 75013 Paris, France.
² Laboratory for Cerebral Dynamics Plasticity & Rehabilitation, Boston University School of Medicine, Boston, MA 02118, USA.
³ Cognitive Neuroscience and Information Technology Research Program, Open University of Catalonia (UOC), 08035 Barcelona, Spain.

Running title: Parietal Rhythmic TMS on vision

Corresponding author (*): Dr. Antoni Valero Cabré, MD PhD, CNRS-INSERM-Université Pierre et Marie Curie. ICM, Equipe Cognition, Neuro-imagerie et maladies du Cerveau; Groupe de Dynamiques Cérébrales, Plasticité et Rééducation. Hôpital de la Salpêtrière, 47-boulevard de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: avalerocabre@gmail.com; avalero@bu.edu
Summary

The intraparietal sulcus (IPS) is a key region of a dorsal fronto-parietal network which together with the frontal eye field (FEF) is engaged during visuo-spatial attentional orienting. Recent evidence in humans has shown that frequency-specific activity patterns on the right FEF in the beta (30 Hz) and gamma (50 Hz) frequency bands modulate, respectively, perceptual sensitivity and response criterion in a conscious visual detection task. Moreover, in non-human primates, the synchronization of these two areas in these same two frequency bands has been found to correlate with top-down and bottom-up attentional processes. Here we tested causally in humans if, in line with these observations, induced rhythmic activity in the right IPS yields frequency-specific effects on conscious visual detection, similar to those reported for the right FEF. Our results reveal a causal association between perceptual sensitivity (d’) enhancements and high-beta parietal activity and also between a shift of response criterion (beta) and gamma parietal induced oscillation patterns. Taken together with the outcomes of our prior study performed in the right FEF, our data suggest that frequency-coded modulations of conscious perception can be induced from either frontal or parietal nodes of the dorsal fronto-parietal network involved in attentional orienting. In addition to these modulations, we observed non-frequency-specific enhancements of perceptual sensitivity in the conscious detection task and accuracy in a forced-choice discrimination task, if a sufficient amount of activity is induced in a critically short time window. These latter effects are possibly mediated by parieto-occipital connectivity and subtended by its ability to operate on the input gain of visual signals.
Introduction

Neuronal synchronization within and between regions of the same network is considered an essential mechanism underlying cognition (Fries 2005). In particular, local and long-range cerebral oscillations within and between frontal and parietal regions have been shown to underlie different processes relevant for perception such as attention (Womelsdorf and Fries 2007), decision-making (Siegel et al. 2011) and conscious access (Dehaene and Changeux 2011).

The intraparietal sulcus (IPS), particularly in the right hemisphere known to be dominant for visuo-spatial processes, is a key node involved in these processes. It is connected to the frontal eye field (FEF) through the first branch of the superior longitudinal fasciculus (SLF I) (Thiebaut de Schotten et al. 2011). Neuronal synchronization in the monkey’s FEF and the lateral intraparietal (LIP) area has been shown to be increased in the high-beta band (around 30 Hz) during top-down attentional orienting and in the gamma band (around 50 Hz) during bottom-up attentional orienting, providing evidence on how top-down and bottom-up processes could be coded along the same fronto-parietal network based on oscillation frequency (Buschman and Miller 2007). In a previous study, we showed that activity noninvasively induced in the human right FEF at these two frequencies modulated different behavioral outcomes (Chanes et al. 2013). More specifically, high-beta (30 Hz) activity selectively enhanced perceptual sensitivity in a conscious detection task without any changes in response criterion, while gamma (50 Hz) activity selectively shifted response criterion in the same task without any modulation of perceptual sensitivity. Based on these studies, we hypothesized that frequency-specific patterns in the right IPS would yield similar perceptual modulations.
Using short bursts of transcranial magnetic stimulation (TMS), we tested the impact of right parietal high-beta and gamma activity on visual performance. Selective effects on perceptual sensitivity and response criterion by these two frequency bands respectively would provide causal evidence that perceptual modulations of conscious perception can be yielded from different nodes of the same network, while different results would emphasize the importance of the level of the network at which activity is induced. Furthermore, we hypothesized that the close direct reciprocal interaction of the posterior parietal cortex with occipital regions could result in further effects on perception, including non-frequency-coded modulations of conscious detection or other perceptual processes such as forced-choice orientation discrimination. The comparison between frequency- and non-frequency-specific patterns (equally long and with equal intensity and number of pulses) allowed us to isolate the effects of frequency from those linked to the amount of activity induced in a given time window.

**Materials and methods**

Two groups of 14 right-handed participants (7 women and 7 men in both groups) aged between 21 and 31 years old (24±3) took part in the experiments. Thirteen of them were naïve as to TMS and to the purpose of the experiment. They all participated voluntarily and reported no history of neurological or psychiatric disorders and normal or corrected-to-normal vision. 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*).

**Apparatus, stimuli and procedure**
Visual stimuli were displayed on an eye-tracker screen (Tobii TX300, Tobii Technology AB) using a laptop computer (Dell Latitude E6400) and standard stimulus presentation software (E-prime). Each trial started with a grey resting screen (luminance: 75 cd/m2, 2500 ms), followed by a fixation screen (randomly lasting between 1000 and 1500 ms) (Chapter VI - Figure 1a). The fixation cross (0.5x0.5°) was displayed in the center, along with three rectangular placeholders (6.0°x5.5°): 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 (0.7x0.7°, 67 ms) to alert participants of an upcoming event. After an inter-stimulus interval (233 ms), a target could appear at the center of one of the two lateral placeholders 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, minimum and maximum Michelson contrast of 0.03 and 0.18, respectively) with its lines tilted 1° to 10° clockwise or counterclockwise from the vertical orientation. The inter-trial interval lasted at least 4 seconds.

Participants were asked to execute two tasks. First, they had to determine the orientation of the Gabor lines (discrimination task) by pressing the corresponding button on a computer keyboard (“1” for counterclockwise and “2” for clockwise) with the index and middle fingers of their right hand. Participants were forced to guess a response even when the target was not presented or they did not consciously perceive it and accuracy was collected as the outcome measure. Secondly, they had to report whether they 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 arrow 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 given key (“d” or “c”) to select the upper or lower arrow pointing to the placeholder (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. Perceptual sensitivity is a bias-free measure that informs on the participants’ ability to detect weak signals in situations that might be strongly influenced by belief. Response criterion describes the relative preference of participants for one response over the alternative one, independently on signal strength. To compute these measures, trials in which the location of the target was correctly determined by participants, were considered as correct detections or “hits” and trials in which participants reported a location for targets that were not presented were considered “false alarms”. Trials in which the location of a present target was incorrectly reported were counted as “errors”. Eye movements were monitored for fixation control purposes (Tobii TX300). Fixation was considered broken when participants’ eyes position was recorded outside the central placeholder (i.e. 3° away from the fixation cross horizontally and 2.75° vertically).

A titration procedure performed prior to experimental trials allowed us to determine, for each participant, the stimulus contrast at which ~50% of the displayed targets were consciously reported. The degree of line tilting was also adjusted individually to maintain discrimination performance at ~75% of correctly reported targets. Such titration levels ensured that in both tasks, performance was halfway between the worse (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 degree of line tilting were adjusted in order to converge to the pre-established criteria. The experiment started once performance levels reached titration criteria and throughout experimental trials stimulus parameters were automatically adjusted every 20 trials (in steps of 0.07 Michelson contrast and 1° of tilting, respectively) to maintain those levels.

Each experimental block consisted of 200 trials, including 40 trials in which the target was absent. In half of the trials, a short pattern of 4 TMS pulses was delivered on the right FEF (active TMS trials). In the other half (sham TMS trials), the same short pattern was applied by a second TMS coil placed next to the stimulation site, with the coil’s surface perpendicular to the scalp, preventing the magnetic field from reaching the skull and stimulating the brain. The order of active and sham TMS patterns was randomized across trials in sub-blocks of 20 trials. Participants were allowed to take a short break and received feedback on the screen about performance and eye movement rates every 40 trials.

We explored the effects of two different stimulation frequencies, high-beta (30 Hz) and gamma (50 Hz), on visual performance in two groups of participants. Each participant of each group performed two experimental blocks of trials the order of which was counterbalanced across subjects. In the frequency-specific block, the 4 TMS pulses were delivered uniformly in time, whereas, in the corresponding non-frequency-specific block, the same 4 pulses were unequally distributed over the same time window (the first and last pulses occurred at identical timing as in the frequency-specific block, whereas the second and third pulses were slightly anticipated and delayed respectively, Chapter VI - Figure 1b). After the titration and
before the two experimental blocks, participants performed a few short blocks of familiarization in which they performed the task with the stimulation.

**Transcranial Magnetic Stimulation (TMS)**

TMS pulses were delivered using a biphasic repetitive stimulator (SuperRapid) with a 70 mm diameter figure-of-eight coil. A structural T1-weighted MRI scan (3T Siemens MPRAGE, flip angle=9, TR=2300 ms, TE=4.18 ms, slice thickness=1mm) was acquired for every participant at the CENIR MRI center (Salpêtrière Hospital, Paris). The right IPS region was localized on each individual MRI using averaged Talairach coordinates x=16, y=-63, z=47 (Kincade et al. 2005) and a 0.5 cm radius spherical Region of Interest (ROI). The marked MRI was uploaded into a frameless stereotaxic system and reconstructed in 3D for its use in an online stereotaxic TMS neuronavigation system (Brainsight, Rogue Instruments) (Chapter VI - Figure 1c).

At all times, the TMS coil was held tangentially to the skull, with its handle oriented ~45º in a caudal-to-rostral and lateral-to-medial orientation, i.e. ~perpendicular to the central sulcus. Coil position was tracked online throughout the experiments and kept steady within an area of ~1-2 mm radius from the targeted site by means of the neuronavigation system. The representation of the right and left primary motor cortex (M1) of the *abductor pollicis brevis* (APB) muscle was localized and the motor thresholds at these sites were determined as the TMS intensity yielding thumb twitching responses in ~50% of the attempts.

Stimulation intensity was set up at 45% of the TMS machine maximal output, for which no involuntary facial muscle activation, blinks and other types of facial sensations induced by field spread were observed. This intensity corresponded to 74% of the mean individual motor threshold.
Chapter VI - Figure 1. Experimental design. (a) Following a central fixation screen, a low-contrast near-threshold target (Gabor stimulus) could be briefly presented within the left or right peripheral placeholders. Participants were asked to perform two tasks: first, a forced-choice line orientation discrimination task (clockwise/counterclockwise); second, a conscious detection task (did you see the target? no/yes and if yes, in which of the lateral boxes). (b) Schematic representation of the temporal distribution of the 4 pulses in the different patterns. (c) Coil positioning on the right IPS.
Data analyses

Trials in which participants broke fixation (2±5%) were eliminated from the analyses. Eye movements could not be recorded in one participant because the eye-tracker failed to detect her gaze.

Each outcome measure (perceptual sensitivity and response criterion for the conscious detection task and accuracy for the discrimination task) for each frequency (30 and 50 Hz) was subjected to a 2x2x2 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 to errors (1.4% and 1.6% of reported targets in the 30 and 50 Hz experiment respectively), which were excluded from the main analyses. An interaction between block and target location was observed for the 30-Hz experiment (F(1,13)=4.85, p=0.046), indicating that in the frequency-specific block participants made more errors for left than right targets, while there were no differences between left and right in the percentage of errors in the non-frequency-specific block. In the 50-Hz experiment, a main effect of TMS was observed indicating that participants made fewer errors with active than sham TMS (F(1,13)=5.94, p=0.03).

Results

For the detection task, participants’ mean perceptual sensitivity (d’) was 1.9 (SD: 0.2) and the mean response criterion was 6 (SD: 1). Participants’ general accuracy (mean±SD) in the discrimination task was 63±11%. It was high when they reported to have seen the target (76±9%), whereas they remained at chance levels when they reported to have not seen it (50±1%).
In the conscious detection task, perceptual sensitivity was modulated by active 30 Hz but not its corresponding matched non-frequency-specific pattern (marginally significant interaction between block and TMS condition, F(1,13)=4.48, p=0.054, Chapter VI - Figure 2 top left). Perceptual sensitivity was higher for active than for sham 30-Hz TMS (planned comparison active vs. sham TMS for the frequency-specific block: F=5.20, p=0.040), whereas no differences between active and sham were observed for the non-frequency specific pattern (planned comparison active vs. sham TMS for the non-frequency-specific block: F<1). This result is analogous to previously reported effects in the right FEF (Chanes et al. 2013). The interaction between block, target location and TMS condition reached significance for response criterion (F(1,13)=5.59, p=0.034, Chapter VI - Figure 2 bottom left). However, planned comparisons between active and sham TMS for left and right targets in either block did not reach significance (frequency-specific block left targets: F=1.21, p=0.292; frequency-specific block right targets: F<1; non-frequency-specific block left targets: F<1; non-frequency-specific block right targets: F=2.38, p=0.147).

In the discrimination task, when all trials were included in the analysis (i.e. correctly-consciously-detected-target and undetected-target trials, thus perceptual forced-choice discrimination independently of conscious access), no main effects or interactions were observed (Chapter VI - Figure 3 top left). However, when only correctly-consciously-detected-target trials were considered in the analysis, the interaction between target location and TMS condition was marginally significant (F(1,13)=4.68, p=0.050, Chapter VI - Figure 3 bottom left), suggesting that TMS improved accuracy ipsilaterally (i.e. for right but not left targets), although planned comparisons between active and sham TMS did not yield significance (F=3.73, p=0.075 and F=2.54, p=0.135, for right and left respectively).
Chapter VI - Figure 2. Impact of 30 (left) and 50 (right) Hz activity and their corresponding non-frequency-specific patterns on perceptual sensitivity (top) and response criterion (bottom) in the conscious visual detection task for active (red) and sham (blue) TMS separately for the left (L) and the right (R) visual fields (VF). Thirty Hz selectively impacted perceptual sensitivity while 50 Hz selectively impacted response criterion. An additional frequency-independent effect was observed: sufficiently powerful activation (50 Hz and its matched non-frequency specific block) enhanced perceptual sensitivity.

Both frequency-specific 50 Hz and the corresponding non-frequency-specific right posterior parietal patterns improved perceptual sensitivity in the conscious detection task as compared to sham (main effect of TMS, F(1,13)=15.23, p=0.002, Chapter VI - Figure 2 top right). For the response criterion, no main effects or interactions reached statistical significance. Although the interaction between block
and TMS condition was not significant (F(1,13)=2.74, p=0.122, Chapter VI - Figure 2 bottom right), we performed a planned comparison between active and sham TMS separately for each block on the basis that our right-FEF prior study had shown frequency-specific modulations of response criterion by 50-Hz activity (Chanes et al. 2013). These comparisons revealed that frequency-specific (F=14.79, p=0.002) but not non-frequency-specific (F<1) patterns reduced response criterion, which is analogous to the results reported for stimulation in the right FEF.

Chapter VI - Figure 3. Impact of 30 (left) and 50 (right) Hz activity and their corresponding non-frequency-specific patterns on general accuracy (top) and accuracy of consciously correctly detected targets (bottom) in the discrimination task for active (red) and sham (blue) TMS separately for the left (L) and the right (R) visual fields (VF). A frequency-independent effect was observed: sufficiently
powerful activation (50 Hz and its matched non-frequency specific block) enhanced accuracy independently on conscious access.

In the discrimination task, when all trials were included in the analysis (i.e. correctly-consciously-detected-target and undetected-target trials, thus perceptual forced-choice discrimination independently on conscious access), a main effect of TMS was observed (F(1,13)=5.04, p=0.043, Chapter VI - Figure 3 top right), indicating better performance with active than sham TMS patterns. No main effects or interactions were observed when only correctly-consciously-detected-target trials were considered (Chapter VI - Figure 3 bottom right).

**Discussion**

Our data demonstrate frequency-specific effects of right posterior parietal activity on visual performance analogous to those previously reported for the right frontal cortex (Chanes et al. 2013). Frequency-specific high-beta (30 Hz) patterns but not its matched non-frequency-specific pattern delivered to the right IPS enhanced participants’ perceptual sensitivity. In contrast, 50 Hz activity in the same location but not its matched non-frequency-specific activity pattern relaxed participants’ response criterion (i.e. participants became less conservative). These results show that the temporal dynamics characterizing patterns of right parietal neural activity are a key factor to explain and understand its contributions.

The right FEF and IPS are key sites of the dorsal attentional network (Corbetta et al. 2002; Corbetta et al. 2008). Prior evidence has shown that neuronal synchronization at high-beta and gamma frequencies in these two areas correlate respectively with the engagement of top-down and bottom-up attention (Buschman and Miller 2007). Furthermore, recent unpublished data from our laboratory show that
the effects of frequency-specific activity in the right FEF correlate with the volume of
the first branch of the superior longitudinal fasciculus (SLF I) linking these two areas,
which together with the fact that the effects described here are in accordance with
those yielded by top-down and bottom-up attention in prior work using similar tasks
(Chica et al. 2011), suggest that TMS patterns at these frequencies in these two
areas might reflect top-down vs. bottom-up attentional processes that impact
differently our conscious detection task.

Interestingly, additional effects were observed in this study. Both 50 Hz and
the matched non-frequency-specific pattern improved perceptual sensitivity in the
conscious detection task and accuracy in the discrimination task. Given that the
activation itself (i.e. either in a frequency- or non-frequency-specific pattern) was not
sufficient to yield these effects when the pulses were distributed in a larger time
window (30 Hz and matched non-frequency-specific block), this results suggest that a
sufficiently powerful activation of the IPS, defined as the amount of activation (i.e.
number of pulses) divided by the time period in which it is delivered (i.e. time
between the first and last pulses), can yield perceptual improvements independently
on frequency or at least in a broader band (including at least 50Hz and the
frequencies embedded in the control pattern). The fact that the effect on accuracy
was observed when all targets (correctly detected and undetected) were taken into
account, suggests that a sufficiently powerful activation improves perception rather
than selectively affecting conscious access. These perceptual improvements may
result from the rich reciprocal connections of the IPS with visual areas, which may
allow an important interaction between TMS and bottom-up activity. Indeed,
differences in the influence of frontal vs. parietal TMS bursts to the visual cortex have
been described. While parietal TMS effects in visual areas appear to depend on the
current visual input, frontal TMS effects do not depend on the presence of visual stimuli but rather differ between central and peripheral locations (Ruff et al. 2008). These differential effects, as the ones reported here, might reflect distinct functional signatures of these two regions.

In sum, our data extend to the right posterior parietal cortex the frequency-specific effects on conscious visual performance reported in prior work for a right frontal area and provide evidence of perceptual enhancements by a sufficient amount of activation in a short time window, possibly thanks to the rich connection of the stimulated region to visual areas. Future studies using concurrent TMS-EEG will address the exact way in which the induced patterns interact with ongoing neural activity.

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Chapter VII
Discussion
VII.I. Overview and summary of the main results

The general goal of this thesis was to study the role and temporal dynamics of fronto-parietal activity patterns on perceptual performance and explore the possibility to use such knowledge to design future interventions that could serve to induce visual performance enhancements in healthy participants or neurological patients. For this purpose, we used visual perception as a testing bench to investigate the influence of frontal and parietal areas in perceptual processes. Noninvasive neurostimulation allowed us to establish causal relationships between specific spatiotemporal neural activity patterns and behavior. This general goal was achieved through an investigation articulated in three main aims in which the general hypothesis was that fronto-parietal systems and their activity subtend and hence influence the modulation of perceptual performance and that the spatiotemporal dynamics of this activity plays a key role in such impact.

Our first aim was investigated in the experiments described in Chapter II. We explored the impact of pre-target activity in the right FEF (i.e. FEF activity before visual stimulus onset) on the discrimination and conscious detection of low-contrast near-threshold stimuli by delivering a single pulse of TMS prior to the presentation of the target, alone (either 80, 100 or 140 ms pre-target onset) or after the display of a peripheral predictive visuo-spatial cue likely engaging the fronto-parietal attentional network (80 ms pre-target onset) (Chanes et al. 2012). Our data show that pre-target FEF activity is relevant for conscious perception as its modulation by TMS impacted conscious detection performance. More specifically, perceptual sensitivity was improved by pre-target single-pulse TMS, particularly when the pulse was delivered closer to target onset. The results also show that neuronal activity within the right FEF is shaped by visuo-spatial attention, as the effect of single-pulse TMS on
perception was modulated by the validity of the trial. Indeed, when delivered before the target onset but after the presentation of a cue, the TMS pulse improved perceptual sensitivity only when the cue correctly predicted the location of the target (valid trials). FEF neuronal subpopulations coding for attended locations (i.e., those relevant for valid trials) have been shown in the monkey to increase their activity and keep it increased during the cue-to-target period (Armstrong et al. 2009). In the case of our study, this implies that TMS would have preferentially affected the most active FEF populations and acted weakly on remaining units. It is through mechanisms of this sort that the neurostimulation of a large area can be shaped at the subpopulation level (Silvanto et al. 2008).

It is well established that brain cognitive functions are not coded simply on the basis of regional and network activations and deactivations but that the fine temporal dynamics of such processes and particularly local and interregional cerebral oscillations play an important role. Hence in our second aim (Chapters III, IV and VI) we addressed the impact of specific spatiotemporal activity patterns delivered to the right FEF, the left FEF and the right IPS on visual performance, and aimed to provide causal evidence of pattern-coded modulations of perceptual performance.

In a first study (Chapter III), we explored the effects of FEF short-burst TMS over the right FEF at specific frequencies (30 Hz and 50 Hz) in the discrimination and conscious detection of low-contrast near-threshold targets (Chanes et al. 2013). A double dissociation between stimulation frequency and modulated behavioral outcome was observed, with 30 Hz activity selectively improving perceptual sensitivity (d’) with no changes in response criterion and 50 Hz selectively relaxing criterion (beta), without inducing modulations of perceptual sensitivity. We demonstrated that such effects were specifically linked to the frequency content of
the stimulation patterns rather than to the total amount of activity yielded by the
bursts, as no effects were observed when the temporal distribution of the patterns
was slightly different, yet equivalent in number of pulses, duration, timing with
regards to target onset and TMS intensity. This study provided causal evidence that
different behavioral outcomes can be impacted from a single cortical area in a
frequency-coded manner, what could reflect a general brain mechanism to multiplex
functions within the same brain region and network. In a second study (Chapter IV),
30 Hz bursts and equivalent non-frequency-specific bursts were delivered this time to
the left FEF and participants were requested to perform the same behavioral tasks. In
this case, no effects linked to the 30 Hz frequency were observed, and instead
perceptual sensitivity (d') was improved by non-frequency-specific patterns, matched
in burst duration, TMS intensity and number of pulses. Together with the results in
the right homotopic area, these data suggest hemisphere-specific coding strategies
for the modulation of visual perception, with the right hemisphere modulating
perceptual sensitivity through high-beta activity patterns, probably reflecting
attentional orienting processes, and the left one modulating the same behavioral
correlate through stochastic facilitation, subtending the same or a different cognitive
process. Finally, the same design of Chapter III was performed on the right IPS
(Chapter VI), which, together with the FEF, is an important component of the dorsal
attention network and known to increase its synchrony at a beta and gamma
frequencies during top-down and bottom-up attentional orienting processes,
respectively, in non-human primates (Buschman and Miller 2007). Such investigation
revealed effects of active 30 and 50 Hz TMS bursts on conscious perception tasks
analogous to those induced by the same frequency-specific patterns delivered over
the right FEF (i.e. enhancement of perceptual sensitivity and shift of response
criterion, respectively). In addition, the more powerful activation (i.e. more pulses per unit of time) of the 50 Hz burst and its matched non-frequency-specific pattern proved able to enhance perceptual sensitivity, as well as accuracy in the discrimination task when all targets (consciously detected and undetected) were considered.

In addition to the frequency, the phase of cerebral oscillations has also been shown to be relevant for behavior and cognition. Our third aim, addressed in the study reported in Chapter V, assessed the impact of the phase of frequency-specific frontal oscillations with regards to target onset on their effect on visual performance. A 30 Hz burst was delivered to the right FEF and participants were again requested to perform a discrimination and a conscious detection task involving low-contrast near-threshold targets. Across 5 separate blocks, 4-pulse TMS bursts were delivered at 5 different phases (i.e. different time lags between the last pulse of the pattern and target onset) within one oscillation period (last pulse delivered from ~17 to 50 ms pre-target onset), every quarter of a cycle (i.e. ~8 ms). The effects of 30 Hz activity on perceptual sensitivity observed in a prior study (Chapter III) appeared to be phase-independent and not to reach significance if the last pulse was delivered too far from the onset of the target. Interestingly, an effect on response criterion appeared for alternate oscillation phases, particularly for longer time intervals between the last pulse and target onset. This effect on criterion, together with prior evidence that this parameter is selectively modulated by gamma oscillatory activity, could indicate cross-frequency interactions between 30 Hz and 50 Hz activity.

VII.II. Frontal and parietal contributions to perceptual performance through characteristic spatiotemporal activity patterns: Implications of our results for
the current ideas on neural dynamics as a key factor for brain function and its noninvasive manipulation in humans

Taken together, the results presented here show that frontal and parietal areas, in particular the FEF and the IPS, modulate perceptual performance through specific neural activity patterns that underlie the cognitive processes in which they are involved (e.g. attention). Our results provide an extensive yet not exhaustive mapping of perceptual performance modulations to specific activity patterns in the human brain.

They contribute to the existing literature providing causal evidence in humans that the frequency of neural activity, isolated from the average amount of activation, plays a key role in its function and point out to similar observations for the phase. It has to be noted that some of our results also show that perceptual modulations can also be sensitive to the average amount of induced activity rather than its frequency, or at least arise from activity in a wide frequency band (see Chapter VI, perceptual sensitivity and accuracy effects under both 50 Hz and non-frequency specific patterns). In addition, our experiments served at assessing the malleability of the system and the possibility to manipulate neural coding through noninvasive stimulation methods with the ultimate goal to enhance perceptual performance in the near future, particularly in clinical brain damage conditions.

Evidence that visual performance can be modulated from different areas and through different temporal activity patterns makes our data compatible with models of large-scale highly-distributed networks of cognitive processes relevant for perception, such as attention and conscious access (e.g. (Corbetta et al. 2008; Corbetta and Shulman 2002; Dehaene et al. 1998)). Our experiments were not designed to address which cognitive process underlies a specific perceptual performance
modulation but rather to explore the mechanisms (i.e. neural code) through which neural activity underlying those processes modulate visual perception.

More generally, brain oscillations have been shown in multiple domains of brain function to underlie many brain processes, including attention and access to consciousness but also memory (e.g. (Duzel et al. 2010; Klimesch 1999)) and language (e.g. (Bastiaansen and Hagoort 2006; Mainy et al. 2008)), among other cognitive operations. In this context, the results of this dissertation support evidence of these characteristic spatiotemporal activity patterns as a general mechanism for brain function. Our results emphasize the importance of not only spatial distribution but also the temporal dynamics of brain activity for brain function and cognition. Moreover, they support the need to further enrich a traditional view of brain function based on specific circuits and networks that would be associated to specific processes with a more dynamical model based on largely-distributed transient spatiotemporal patterns of neural activity that could code for several operations in a limited number of neurons. In a context in which studies assessing the neural basis of different cognitive processes often report networks that are highly co-localized (see (Corbetta et al. 2002; Corbetta et al. 2008; Dehaene and Changeux 2011; Siegel et al. 2011) for reviews in attention, consciousness and perceptual decision-making), in line with influential literature published in the last decade and departing from the three influential reviews of Engel, Salinas, Varela and colleagues (Engel et al. 2001; Salinas and Sejnowski 2001; Varela et al. 2001), our data show that cerebral oscillations, characterized by site, frequency and phase, provide an excellent electrophysiological code to multiplex functions within a given neural substrate. Our studies gathered extensive causal evidence that such refined language might cover
the modulation of a broad spectrum of visual behaviors and might ultimately underlie different cognitive operations and processes.

At the same time, our studies aimed to explore the ability of noninvasive stimulation methods, and very particularly TMS, to modulate specific neural activity patterns with the ultimate goal to apply these techniques and procedures in the near future to treat pathological conditions involving specific alterations of neural activity and brain oscillations. TMS proved largely able to modulate brain rhythms with an expected temporal resolution that allows isolating the effects of frequency through precise small temporal variations of the stimulation patterns used. We provide evidence in line with previous work that the effects of TMS depend on the state of activity within the stimulated region and associated networks and that such could be employed through simple visuo-spatial paradigms to shape neurostimulation effects and make them specific to some of the interleaved subpopulations of neurons within the stimulated region (Chanes et al. 2012; Silvanto et al. 2008; Silvanto and Muggleton 2008a; Silvanto and Muggleton 2008b; Silvanto et al. 2007a; Silvanto et al. 2007b; Silvanto and Pascual-Leone 2008).

**VII.III. Pending questions and future directions**

Our studies were designed to maximize the number of conditions tested respecting at all times safety regulations. Notwithstanding, the high technological demands and long duration of our experimental sessions have certainly limited the stimulation parameters that could be probed and the number of conditions that could be tested. Our will to have adequate sham TMS conditions and active TMS control patterns to isolate the effects of frequency from the impact of frequency-unspecific regional activation, significantly increased the duration of the experiments and limited
the number of regions and frequencies tested. Indeed, the delivery of sham and active pulses randomly interleaved required the use of two repetitive TMS machines, which was challenging to have available at the same place and time but provided an outstanding design in which active and sham TMS patterns were embedded in the same block.

Our studies have thoroughly addressed the role of the right FEF with single pulses and the oscillatory basis and phase dependence of its causal contributions to visual discrimination and conscious detection. We have also studied similar oscillation-related effects on the right IPS region and addressed inter-hemispheric differences between the right and left FEF. However, interesting aspects remain unexplored at the end of this thesis and will have to be addressed in the near future in order to provide further detail and complete the general picture of how right and left fronto-parietal systems operate to modulate visual perception. In particular, the role and dynamics of the left IPS in perceptual performance remains unexplored, as well as the role of lower frequencies, like theta (known to modulate gamma through cross-frequency interactions) (Canolty et al. 2006; Jensen and Colgin 2007; Lakatos et al. 2008; Mormann et al. 2005) or alpha (the desynchronization of which at occipital and posterior parietal locations has been associated with visuo-spatial attention) (Gould et al. 2011; Rihs et al. 2007; Sauseng et al. 2005; Thut et al. 2006; Worden et al. 2000).

The requirements of some of the experiments also limited the stimulation parameters that could be used. Although the optimal stimulation intensity is not known, frontal and parietal regions are often stimulated at intensities of 50-65% of the maximum stimulator output (e.g. (Grosbras and Paus 2002; Grosbras and Paus 2003; O'Shea et al. 2004; Romei et al. 2011; Silvanto et al. 2006)). However, in our
experiments using short TMS bursts, we used a fixed intensity of 45%, at which the capacitors of the machine showed capable of recharging on time to deliver each of the 4 pulses of the burst (particularly for the higher frequency, i.e. 50 Hz, for which the pulses were closer). Although our studies show that such “technically-imposed” slightly low levels of intensity induce significant perceptual effects, one could think that higher TMS intensities, as those more widely used, could have been more effective. Notwithstanding, higher intensities are also associated with higher ‘click’ sound and stronger tapping sensation accompanying the pulses, which might interfere more severely with the experiment and be more difficult to control for. Moreover, in the same experiments, we chose to deliver trains of four pulses, as a compromise between an enough trial-by-trial number of induced cycles and, together with long inter-trial intervals, a short-enough stimulation to avoid carry over effects across trials and experimental blocks.

Our choice of a double sequential visual task (conscious detection and forced-choice discrimination) was made with the aim to capture potential modulations of frontal and parietal neural activity to well-known behavioral measures, which represent different aspects of visual function and performance. However, our interventions proved mostly unable to modulate forced-choice discriminations. Only when a sufficient amount of activity was delivered on the right IPS in a short critical time window (corresponding to 50 Hz and its matched non-frequency-specific pattern), TMS stimulation improved discrimination accuracy. We also found improvements of visual discrimination during the stimulation of the right FEF with high-beta TMS patterns when the 4-pulse bursts were delivered in a critical short pre-target time window. In both cases, these effects were found to be independent on conscious access (i.e. observed when all targets, undetected and correctly detected,
we taken into account). Future research will have to address why awareness-independent perceptual modulations were so rarely observed and why conscious processes could not be modulated further than detection (i.e. why conscious discrimination could not be enhanced).

In our first study (Chapter II), inspired by well-characterized versions of this same type of paradigms (Chica et al. 2011), we asked participants to perform as fast and as accurately as possible a forced-choice discrimination task. This was done because both endogenous and exogenous attention are known to consistently decrease reaction times in this task (Chica et al. 2011), what is considered a robust maker of attentional orienting. However, single-pulse right-FEF TMS stimulation, either alone or in combination with spatial cues, proved unable to modulate discrimination reaction times and accuracy, suggesting that such increases in perceptual sensitivity (d’) might not have been mediated by attentional processes. In order to avoid a potential speed-accuracy trade-off that could limit the modulation of visual discrimination and in an attempt to approximate response conditions to those of the conscious visual detection task in which there was no time pressure, for the remaining experiments we asked participants to perform discrimination ‘as accurately as possible’ (as opposed to ‘as fast and as accurately as possible’). This, we thought, would possibly make it easier to observe modulations of discrimination but, at the same time, eliminated the well-studied signature of attentional processes from our studies. Future research will have to address whether perceptual modulations induced by different activity patterns correspond to attentional or other cognitive processes.

Finally, the interpretation of some of our results was limited by the lack of concurrent TMS-EEG recordings. Indeed, such data, which we are currently trying to
develop, will help to elucidate how the TMS pulses delivered interact with ongoing activity and particularly with ongoing oscillations. They will help to quantify the entrainment of oscillations at the frequencies used (Chapters III, IV and VI) and could provide further basis to understand the visual detection stochastic facilitation driven by random arrhythmic left-FEF activity (Chapter IV). Such recordings could also shed further light in the hypothesized potential cross-frequency interactions between high-beta and gamma activity in the right FEF resulting in the modulation of response criterion (Chapter V), and help to better understand how the synchrony of the right posterior parietal (IPS) and the right FEF regions at beta and gamma frequencies interact.

The use of concurrent TMS-EEG has been seriously developed in the last decade thanks to *ad hoc* TMS-compatible EEG equipment, particularly pre-amplifiers, able to clamp recordings during the TMS artifact (e.g. (Virtanen et al. 1999)), to not respond to the very high slew rate of the TMS pulse (e.g. (Thut et al. 2003)) or to not saturate during the TMS pulse thanks to wide dynamic range (e.g. (Bonato et al. 2006)). Nonetheless, it remains very challenging to record artifact-free EEG activity during the short inter-pulse intervals and the key time between the burst end and target onset. Such approaches have however been able to provide at least important evidence of alpha entrainment during 5-pulse 10-Hz bursts with a rapid decay time beyond the duration of the burst (Thut et al. 2011). More challenging is the recording of similar evidence in actively performing participants stimulated at higher frequencies, as the ones used in our studies (i.e. 30 and 50 Hz, with inter-pulse intervals of ~33 and 20 ms, respectively). Additional hurdles that difficult the use of such methods is that combined TMS-EEG behavioral experiments are cumbersome for participants and long, with important preparation time and a high required number
of trials per condition. This limits the number of conditions that can be tested per session. Overall, the use of concurrent TMS-EEG is of course well justified when EEG recordings are essential to prove the hypothesis raised in the study. In absence of concurrent EEG recordings, we have mostly tried to limit our interpretations along the present dissertation to the patterns that were ‘injected’ to the region, rather than base them on the interactions of such patterns with the region’s ongoing activity. We have also made a real effort to emphasize the potential but also the limits of our interpretations, differentiating between proven facts and explanatory hypothesis in attendance of further demonstration.

VII.IV. Perspectives

The relevant role of cerebral oscillations in brain function and cognition has been now studied for more than a decade. Nonetheless, this endeavor just started and in the years to come, the development of novel methods and imaging technologies will permit a noninvasive causal investigation of the many aspects that remain to date controversial or simply unexplored (see (Dayan et al. 2013) for a recent review). In particular, recent low-cost, portable non-invasive neuromodulation devices such as transcranial alternate current stimulation (tACS), for example, may provide an easier and safer way to explore, at the cost of a limited spatial resolution, the causal contribution of characteristic spatiotemporal activity patterns to human cognition in healthy participants and brain-damaged patients. This and other emerging techniques, such as ultrasound or optical stimulation, will certainly combine their efforts with frequency-tailored rhythmic TMS, as used in the current dissertation, to pursue common goals.
In addition, the development of more selective stimulation coils for TMS and other non-invasive brain stimulation tools capable of reaching deeper brain structures will extend to subcortical sites explorations that are now limited to rather superficial brain areas. Most importantly, the combination of noninvasive neurostimulation with neuroimaging techniques able to assess the extent of its impact with an acceptable spatial resolution, and with high-density EEG in online TMS applications and magnetoencephalography (MEG) in offline designs, will provide valuable knowledge on brain function and broaden the interpretation of causal evidence.

The challenges ahead are complex and the stakes high, since the therapeutic potential is enormous and could benefit many. Indeed, brain oscillations have been shown for example to be affected in highly prevalent neuropsychiatric disorders including schizophrenia (Uhlhaas and Singer 2010) and depression (Linkenkaer-Hansen et al. 2005). Similarly, visual target omissions have been correlated recently in right-hemisphere stroke patients suffering visuo-spatial neglect to increases in the power of low-beta oscillations in the left FEF (Rastelli et al. 2013), providing clear clues for the use oscillation-tailored TMS in the rehabilitation of focal brain damage. Overall, a better understanding of impaired brain rhythms and their relation with cognitive function and deficits should encourage the use of noninvasive neurostimulation techniques, first to causally probe their physiological role and later on to better understand its alterations with the ultimate goal to restore the rhythms of the healthy system.
REFERENCES


