PERCEPTUAL CONSEQUENCES OF REFLEXIVE EYE MOVEMENTS: EFFECTS OF EXOGENOUS ATTENTION AND FRONTAL STIMULATION

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Abstract

This thesis investigated the visual perceptual consequences of reflexive eye movements in humans. A multimodal approach involving the modulation of exogenous attention, and the perturbation of the right frontal eye field (rFEF), explored visual perceptual and oculomotor control functions. Stimulation of the rFEF by TMS and the presentation of stimuli (cues) in order to orient attention, were combined with the measurement of brain activity with EEG, and eye tracking. These methods allowed the investigation of brain function and cognitive processing during a task combining visually driven eye movements with visual motion discrimination. Perturbation of the rFEF provided evidence of dissociable roles in visual perception, shown by a facilitatory effect during involuntary eye movements and an inhibitory effect during eye movement suppression. The rFEF TMS effect at the behavioral level was accompanied by posterior alpha power modulation. Not only the visual perceptual but also the oculomotor control function of the rFEF were affected by TMS, as shown by the reduction in eye movement velocity. The modulation of attention by the presentation of cue stimuli led to effects that were not dependent on eye movements: a facilitatory effect of exogenous orienting of attention was observed when the motion discrimination task was performed simultaneously with the generation of reflexive eye movements, and again also during movement suppression. The effect of attention was reflected in EEG correlates of early visual perceptual processing. Taken together, these results allow generalization to real-world contexts or clinical conditions where visual perception may be compromised by involuntary or pathological eye movements, highlighting the fact that even during reflexive movements the potential involvement of attention is essential for understanding cognitive processing.

Abbreviations

BOLD	Blood oxygen level dependent
EEG	Electroencephalography
ERP	Event related potentials
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
FPA	Frontal pursuit area
ICA	Independent component analysis
OFRs	Ocular following reflexes
OKN	Optokinetic nystagmus
OKS	Optokinetic stimulation
PIVC	Parietoinsular vestibular cortex
rFEF	Right frontal eye field
rM1	Right primary motor cortex
ROI	Region of interest
STFT	Short time fourier transform
TEP	TMS-evoked potentials
TMS	Transcranial magnetic stimulation
VOR	Vestibulo-ocular reflex

1. Introduction

1.1 A stable world for “unstable” eyes

Our eyes are never stationary and yet nevertheless we still perceive stable visual scenes. The challenge for our visual system is to separate optic flow due to an eye movement from optic flow resulting from self-motion (Angelaki and Hess 2005a). The perceived motion of visual objects as the eye or the observer move help us to navigate our environment. The projects described in the following sections explored situations in an important respect comparable, even though in a laboratory setting, to what is experienced in our everyday life, when perceptual judgments are made, and our eyes are not fixating on an empty visual screen, as often is the case during experiments measuring visual perception. Instead our eyes respond to the optic flow that is generated when we move. To perceive a stable world, visual stabilization mechanisms known as ocular following reflexes (OFRs), which are visually driven responses, are driven by the need to re-establish a stable visual input on the retina eliminating residual retinal slip (Angelaki and Hess 2005). The focus of this dissertation is on the visual perceptual consequences of reflexive eye movements. First we investigated the role of the frontal eye field (FEF) in this context, and the FEF contributes to both ocular motion and visual perception. Following this, the manipulation of exogenous attention was explored in order to understand the importance of orienting of attention in situations where - despite reflexive eye movements - perceptual judgements are needed.

1.1.1 The frontal eye field in eye movements and visual perception

The frontal eye field (FEF), located in the frontal cortex, and is a brain region capable of triggering eye movements when electrically stimulated. The primate FEF has been located in the frontal lobe adjacent to the anterior part of the arcuate fissure, corresponding to Brodmann's area 8, or to the overlap between 8 and 6 in humans (see Tehovnik et al. 2000 for review). The human FEF has been defined as being anterior to the intersection of the inferior part of the superior precentral sulcus and the superior frontal sulcus. This location lie in Brodmann's area 6 (Paus 1996). However, it is still not clear whether differences in FEF location may be due to the anatomical difference between non-human primates and humans, or due to interindividual differences related to experimental settings and sample sizes used for animal and human studies (Vernet et al. 2014).

The FEF is not only involved in eye movements but it is also engaged in several aspects of the cognitive domain. Methods such as stimulation or neuroimaging, tasks, and intensity of stimulation used, are all factors that determine the precise location of the FEF (Paus 1996; Blanke et al. 2000). Covert or overt orienting to visual targets led to different responses in macaque FEF neurons. Bruce and Goldberg (1985), in a task where saccades could be associated with visual targets, showed that some neurons were entirely visual in response profile whereas others were entirely motor, but still others may be responsible for higher order functions, as electrical signals could be recorded in response to a visual pre-cue if an eye movement was anticipated. Starting with these pioneering findings, many other studies have demonstrated the FEF contribution in planning saccades (e.g. Thompson et al. 1997; Murthy et al. 2001), covert attention (e.g. Moore and Fallah 2004) and the selection of salient information (Thompson and Bichot 2005 for review). Human studies using transcranial magnetic stimulation (TMS) have shown the causal role of the FEF in facilitating visual perception during detection, improving performance after FEF TMS at target location detection with visual masking (e.g. Grosbras and Paus 2003). Several studies focused on FEF function in a more natural behavioral context extending this to its top-down influences; those studies suggested that visual information might be not encoded if it does not represent the target for upcoming saccade (Burman and Segraves 1994; Fernandes et al. 2014; Ramkumar et al. 2016). FEF activity has been related more to impending eye movements than to visual saliency. Other findings showed the FEF to be implicated in feature-based attention (Bichot and Schall 1999; Zhou and Desimone 2011). The different experimental settings must to be taken into account: during an empirical task only a few saccade targets are made compared to the many that could be made in natural scenes; it has been suggested that feature-based attention might be only relevant to attend to a region of space close to the point of fixation (parafoveal regions). During a search task on natural scenes monkey FEF activity did not reflect feature-based attention but upcoming eye movements, and one explanation is that the FEF, in a natural scene, is more engaged in spatially guided eye movements rather than visual saliency (Ramkumar et al. 2016).

The early anatomical portrait of the FEF is based on non-human primate studies. The multiple and dissociable roles of the FEF are allowed by the numerous connections sent from and to this area. The FEF receives connections from the middle temporal area (MT, Tian and Lynch 1996) and sends connections to several areas, in frontal cortex including supplementary eye fields (SEM, Stanton et al. 1993), the occipital and parietal cortices, and in particular V2/V3/V4, as well as MT, medial superior temporal area (MST) and the superior temporal visual area (Stanton et al. 1995). In addition reciprocal connections have been shown between FEF and parietal cortex, principally with lateral intraparietal area (LIP, Cavada and Goldman-Rakic 1989; Stanton et al. 1995; Tian and Lynch 1996). Subcortically, the FEF projects to the brainstem (Segraves 1992) and receive projections from the cerebellum passing through thalamic regions (Lynch et al. 1994). Finally, connections to the superior colliculus (SC) have been demonstrated directly (Segraves and Goldberg 1987) and indirectly via the basal ganglia (Stanton et al. 1988, as cited in Vernet et al. 2014).

The FEF has not only been described as a crucial brain region for preparation and execution of fast eye movements, such as saccades (e.g. Bruce and Goldberg 1985; Pierrot-Deseilligny et al. 1995) but also for the control of slow eye movements, smooth pursuit or optokinetic nystagmus (OKN, Bizzi 1968; MacAvoy et al. 1991; Dieterich et al. 2003, 2009), and fixation (Izawa et al. 2004b, 2004a, 2009) or suppression of OKN (Dieterich et al. 1998).

1.1.2 Optokinetic nystagmus and FEF

The optokinetic nystagmus (OKN) is a saw-tooth-profile reflexive eye movement performed in response to large visual scenes moving in a coherent way. Purkinje (1825) described for the first time the OKN through the eye movements of an observer that was watching a parade. A slow phase eye movement, performed to stabilize the image of the parade on the observer's retina, was interrupted by frequent resetting quick phase in the opposite direction. The OKN is a reflexive eye movement generated in order to differentiate between self-motion, relative to a stationary environment, and environmental-motion, relative to a stationary viewer. These two perceptual interpretations may also be combined. The optokinetic response to moving surroundings with the slow phase in the visual scene motion direction and resetting saccade in the opposite direction, is crucial for mediating object-motion perception.

A distinction between "look-OKN" and "stare-OKN" rests on two types of eye movements. The first shows similarities with pursuit eye movements and can be generated from attentively viewing a moving stimulus, and the second, stare-OKN, arises from passively viewing a moving stimulus. The stare-OKN is considered fully automatic (Pola and Wyatt 1985) and is characterized by smaller amplitudes and higher frequencies compared to look-OKN (Cheng and Outerbridge 1974; Knapp et al. 2008). The stare OKN occurs reflexively in response to large field retinal motion, with a latency of 100 ms (Gellman et al. 1990). Unlike look-OKN, stare-OKN is not associated with a significant activation of cortical areas (Konen et al. 2005; Ruehl et al. 2019). Nevertheless, eye movements such as saccades and smooth pursuit have been associated with the activation of different cortical structures (Pierrot-Deseilligny et al. 1995; Paus 1996). Further differences are apparent when eye movements are accompanied by a visual motion perception task, and a greater signal has been registered from occipito-temporal cortex during smooth pursuit of moving dots than in viewing moving gratings while keeping the eyes still (e.g. Barton et al. 1996; Dieterich et al. 1998). The OKN can also be generated during small-field optokinetic stimulation. Even though OKN and pursuit eye movements seemed to activate similar brain networks, several studies reported differences between pursuit and optokinetic system (Tusa and Zee 1989; Konen et al. 2005; Bense et al. 2006). Cortical and subcortical activations have been reported in fMRI studies measuring the brain response to optokinetic stimulation: primary visual cortex, motion-sensitive areas in the occipitotemporal cortex and several cortical oculomotor areas above described for the control of saccades, like the FEF, parietal eye field, supplementary eye field and prefrontal cortex were activated bilaterally (Bucher et al. 1997; Dieterich et al. 1998). Later, it has been found that even though the OKN is defined as smooth pursuit-like eye movements interrupted by saccade-like quick phases, its cortical control is not the combination of pursuit and saccade cortical networks, and rather three different subregions of the FEF seemed to be responsible for saccade, pursuit and OKN (Dieterich et al. 2009). In this study, the oculomotor control networks were investigated using three different oculomotor tasks including saccade, pursuit and OKN. This approach intended to define the shared and unshared cortical networks related to these three paradigms, and findings showed that there was a specific cortical control of OKN that was missing during saccade and pursuit, especially in frontal regions: FEF activation was stronger during optokinetic stimulation in the right hemisphere in right-handers (Dieterich et al. 2009).

In addition, BOLD signal changes were observed during small-field optokinetic stimulation in retroinsular and insular regions, described as the human homologue of the parietoinsular vestibular cortex (PIVC) in monkeys. The PIVC, considered the core of the vestibular cortical system, presented bilateral deactivation in humans (Brandt and Dieterich 1999) and in non-human primates (Guldin and Grüsser 1998). Interestingly, several fMRI studies showed a reciprocal inhibitory visual-vestibular interaction induced by optokinetic stimulation, with BOLD signal increases in the visual cortex and in oculomotor control areas, including the FEF, and BOLD signal decreases in the PIVC (Brandt et al. 1998; Deutschländer et al. 2002; Dieterich et al. 2003). This activation-deactivation pattern during OKN has been investigated in patients with vestibular loss (Dieterich et al. 2007; Deutschländer et al. 2008) and in healthy controls (Brandt et al., 1998; Dieterich et al., 2003; Konen et al., 2005). Vestibular patients showed stronger activation of MT/V5 and right FEF compared to control subjects (Dieterich et al. 2007). Evidence regarding the involvement of frontal areas in slow eye movements comes from TMS studies, where the stimulation of a frontal pursuit area (FPA) immediately before a target moving horizontally reversed direction, increased the eye velocity in the new direction during a smooth pursuit task (Gagnon et al. 2006). Eye velocity changes following the stimulation of FPA have been also observed in animal studies (e.g. Gottlieb et al. 1993). FEF stimulation delayed contralateral pursuit eye movements, especially during pursuit of unpredictable target motion (Drew and van Donkelaar 2007).

1.1.3 Link between covert attention and reflexive eye movements

A further question addressed in this thesis relates to the link between the mechanism for shifting the eyes and shifting attention. The visually driven shifting of the eyes, as occurs during optokinetic stimulation, is similar to what we experience when we move in our environment: the relationship between reflexive eye movements and the orienting of covert attention might be crucial to allow an adequate perception of visual stimuli. Visual objects can indeed be examined without overtly looking at them, but simply by covertly directing the attention to them.

Attention is the mechanism by which "objects" are selected and this may occur in a voluntary or in an involuntary way (Theeuwes 1994a, 1994b). Two different types of attention were initially described by William James (1890), one reflexive or passive and the other one active, and these are now described as endogenous and exogenous attention (Posner 1980a). The former refers to a "top-down" shift of attention that requires cognitive process, and to our ability to monitor information at a given location, whereas the latter refers to a "bottom-up" shift of attention that is automatic and externally driven, such as the orienting to a location following sudden stimulation. Covert attention is oriented to areas in the periphery without looking at them directly (described for the first time by Helmholtz 1896). In many situation we rely on covert attention, for example while we are driving or crossing the street. Spatial attention has been described as a "spot-light" (Posner, 1980) or "zoom-lens" (Eriksen and St James 1986) that selectively raises the processing of stimuli present in the area of focus. The change of an observer's attentional state while an image is kept constant on the retina may affect perceptual performance and neural activity in the visual cortex and visual attention seems to be responsible for these processes (Carrasco 2011).

Over time studies have focused mainly on the relationship between covert attention and saccade programming (Goldberg and Wurtz 1972; Wurtz and Mohler 1976; Eimer et al.

2007; Smith and Casteau 2019). Attention has been proposed to be equivalent to generating a motor response, such as eye movements. This was supported by earlier research, first under the *oculomotor readiness hypothesis* (Klein 1980) and later by the *premotor theory of attention* (Rizzolatti et al. 1987), according to which visual attention reflects the programming of eye movements. Additional evidence for a relationship between covert visual attention and eye movements came from dual task experiments: during saccade preparation an automatic shift of attention occurs to the end point of a saccade not yet executed (Deubel and Schneider 1996; Montagnini and Castet 2007; Kowler 2011a). The attentional effects of primate FEF stimulation which also influenced visually-guided saccades were demonstrated in a study measuring the effect of visual motion on target position (Schafer and Moore 2007). Many saccade-related neurons fired early and during saccades executed in order to bring visual stimuli into their receptive fields (RFs, Duhamel et al. 1992; Sommer and Wurtz 2006). Even though the literature offers a growing body of evidence for the relationship between saccades and covert attention, in daily life it is arguably no less important to update the processing of visual scenes during slow eye movements. In the domain of voluntary eye movements, attention and oculomotor preparation for the impending eye movement seem to share a similar control mechanism. It is important now to extend our focus to the link between attention and other type of eye movements: slow eye movements such as smooth pursuit and OKN, and in general to involuntary eye movements. Indeed, slow changes in direction of visual stimuli, like what occur during smooth pursuit, do not suppress visual input like what happens during fast eye movements like saccades (Bridgeman 2011). Visual responses showing a continuous updating of the visual scene were reported during smooth pursuit, and this response was task dependent (Dash et al. 2015).

Motion of the visual field during eye movements (reafference) is one of the signals available for visual stability together with proprioception and corollary discharge (Wurtz 2008).

Recent studies showed that OKN can be modulated by attention (Williams et al. 2006a; Rubinstein and Abel 2011a), for instance when two pattern of dots moved in the peripheral visual field, OKN responses were increased to the moving pattern that was in the focus of attention. In that study, two motion stimuli, patterns of moving dots inducing OKN, were presented on either side of a fixation cross or above or below it; a visual cue indicated which of the two moving stimuli participants had to attend to. They were asked to perform an attentional task that consisted of counting the targets of white dots while keeping their eyes on the center. The frequency and the gain (ratio of the slow phase velocity to stimulus velocity) of OKN increased when the moving pattern in the peripheral visual field was the focus of attention (Kanari et al. 2017a).

1.1.4 Oscillopsia: a "blurred" world

Oscillopsia is a pathological condition often associated with vestibular lesions and it is characterized by blurred vision due to uncontrolled eye movements. Even though it normally occurs only in the acute phase of the illness this is a severe condition that compromises the everyday life of patients. The vestibular-ocular reflex (VOR) generates gaze stabilization during head movements. Patients that suffer from vestibular pathology, especially bilateral vestibular failure (BVF), lose this ability and experience an illusory movement of the visual scene, oscillopsia (Rinne et al. 1998). Oscillopsia is often studied to understand the relationship between visual and vestibular systems. Several studies have demonstrated that in the normal state the visuo-vestibular balance is preserved by a reciprocal inhibition, whereas in vestibular loss a reduced vestibular inhibition of visual signals occurs resulting in visual dominance (Roberts et al. 2013). Neuro-physiological findings in BVF patients, with total loss of vestibular functions, showed that the down-regulation of the excitability of the visual cortex, measured with TMS of the visual cortex, was also associated with a reduction of oscillopsia related symptoms (Ahmad et al. 2017a). The consequences of the asymmetry between vestibular and visual system seem to be wide-ranging. Indeed, fMRI studies suggest different strategies following vestibular loss, such as visual substitution for missing vestibular input (Dieterich et al., 2007) and suppression of visual motion perception as an adaptive mechanism to reduce oscillopsia (Deutschländer et al., 2008). Spontaneous nystagmus, an abnormal eye movement, is associated with the acute phase of vestibular failure (Becker-Bense et al. 2014). The monitoring of brain activity during acute and chronic phases of vestibular damage provide evidence of a reorganization of multisensory vestibular cortex and oculomotor areas, including the FEF. Oculomotor control and visual areas were more active immediately after vestibular loss, whereas in the chronic phase patients showed decreased activity in these areas during optokinetic stimulation.

Given that FEF activation seem to depend on the phase of the pathology and therefore on the level of visual perceptual damage, the FEF might play a role in oscillopsia. Considering that the FEF has both oculomotor control and visual perceptual functions, the impaired visual perception that occurs after vestibular lesions might be not only due to abnormal eye movements: the impairment of the covert attentional mechanism might also be the cause of a blurred vision.

1.2 Aim of the thesis

The objective of this dissertation was to investigate how we manage to have successful vision despite dealing with the perceptual consequences of reflexive eye movements. The necessity of the investigation of human brain in “natural” contexts is becoming more and more prevailing in the community of neuroscience (Krakauer et al. 2017a; Taylor 2018a). A multi-technique approach including TMS, EEG and eyetracking combined with a novel task where visual perceptual discrimination was required during reflexive eye movements were used in these studies. The goal of these complex experiments has been the investigation of human cognition during situations beyond the conventional lab context, to allow the generalization of the findings to real-world contexts and also to clinical situations where pathological eye movements compromise visual perception.

The aim of the first study was the investigation of the causal role of the FEF in dealing with the perceptual consequences of reflexive eye movements, OKN, induced by a moving visual scene. TMS FEF effects on behavior clarified the role played by this brain area in increasing visual discrimination during reflexive eye movements. Brain activity changes were first investigated while participants were fixating on a moving background (see Chapter 2.1) and later further analyses were performed on brain activity during OKN (see Chapter 2.2).

In the third study (see Chapter 2.3) the orientation of attention was examined during the same task, and the FEF TMS was replaced with the manipulation of exogenous attention in order to understand the attentional mechanism behind our ability to form a clear percept of stimuli that we are surrounded by despite the fact that the eyes are rarely stationary when we move in our environment.

2. Cumulative Thesis

This doctoral thesis consists of three studies: one peer reviewed and published article (**2.1**) and two detailed manuscripts (**2.2** and **2.3**). The following chapters consists of these study.

2.1 Study 1: Right Frontal Eye Field has perceptual and oculomotor functions during optokinetic stimulation and nystagmus

The following chapter has been published as Mastropasqua A, Dowsett J, Dieterich M, Taylor PCJ. (2019) Right Frontal Eye Field has perceptual and oculomotor functions during optokinetic stimulation and nystagmus. *J Neurophysiol*.

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Right Frontal Eye Field has perceptual and oculomotor functions optokinetic stimulation and nystagmus

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Abstract

The right frontal eye field (rFEF) is associated with visual perception and eye movements. rFEF is activated during optokinetic nystagmus (OKN), a reflex that moves the eye in response to visual motion (optokinetic stimulation, OKS). It remains unclear whether rFEF plays causal perceptual and/or oculomotor roles during OKS and OKN. To test this participants viewed a leftward moving visual scene of vertical bars and judged whether a flashed dot was moving. Single pulses of transcranial magnetic stimulation (TMS) were applied to rFEF on half of trials. In half of blocks, to explore oculomotor control, participants performed an optokinetic nystagmus (OKN) in response to the OKS. rFEF TMS, during OKN, made participants more accurate on trials when the dot was still, and slowed eye movements. In separate blocks, participants fixated during OKS. This not only controlled for eye movements but also allows using EEG to explore the FEF's role in visual motion discrimination. Here, by contrast, leftward dot motion discrimination was impaired, associated with a disruption of the frontal-posterior balance in alpha-band oscillations. None of these effects occurred in a control site (M1) experiment. These results demonstrate multiple related yet dissociable causal roles of the right FEF during optokinetic stimulation.

Keywords: FEF, optokinetic nystagmus, slow eye movements, TMS-EEG, visual perception.

Introduction

The visual system faces a variety of perceptual and oculomotor challenges when confronted with motion in the visual scene. Background motion changes need to be compensated for when trying to ascertain whether smaller foreground objects are moving relative to the observer. Additionally, such optokinetic stimulation can elicit a reflexive eye movement, the optokinetic nystagmus (OKN) (Ilg 1997; Kowler 2011; Purkinje 1825 and Barany 1907 as cited in Bender and Shanzer 1983). This visually driven response originates from the need to re-establish retinal image stability by triggering eye movements, which eliminate the retinal slip that would compromise visual acuity (Angelaki and Hess, 2005). The OKN is characterized by two phases: a smooth eye response in the direction of field motion (slow phase) interrupted by resetting fast eye movements in the opposite direction (quick phase). Although the generation of the OKN involves many subcortical regions (Ruehl et al. 2019), imaging studies of OKN have identified cortical responses including in the right Frontal Eye Field (rFEF) during OKN (Dieterich et al. 1998, 2003, 2009; Konen et al. 2005). The function of these cortical activations, including rFEF, remains unclear, in particular whether these regions are responsible for the OKN itself, for perception of the OKS, or for perceptual consequences of the OKN.

Maintaining stable vision during eye movements requires compensating for the sensory consequences of those eye movements (Wurtz, 2008). Motion of the visual field during eye movements (reafference) is one of the signals available for visual stability (others being proprioception and corollary discharge, Wurtz 2008). If the optic flow generated by eye movements is predicted successfully it can be used to dissociate between self- and environmental-motion (von Holst, E. and Mittelstaedt, H., 1950; Wurtz 2008) and is crucial for spatial navigation (Angelaki and Hess, 2005). Although there has been substantial interest in dissociating whether the FEF is important for eye movements and/or dealing with the perceptual consequences of eye movements, this work has not focused on OKS and OKN but rather mainly on saccades and the use of corollary discharge (Moore and Armstrong, 2003; Moore and Fallah, 2004). It is an important step to extend this to other types of visual stimuli and eye movements because the demands are very different. For example saccadic suppression cannot be used to help visual stability (Bridgeman, 2011) when smooth pursuit eye movements are performed in the presence of a moving background (Haarmeier and Kammer, 2010; Spering and Gegenfurtner, 2007; Spering and Montagnini, 2011). But it remains unclear what functions the rFEF may have in this dynamic context.

Visual motion perception can be impaired after vestibular failure. Patients with vestibular deficits, especially during the acute phase, can experience “oscillopsia”, an illusory movement of the visual world driven by an inability to perceptually compensate for eye movements. Impaired visual motion perception in these patients has been interpreted as evidence for a central mechanism acting to reduce the symptoms of oscillopsia (Ahmad et al., 2017; Grünbauer et al., 1998; Shallo-Hoffmann and Bronstein, 2003), suppressing visual motion processing in an attempt to direct attention to specific objects presented in their environment. Activations including the rFEF were found in vestibular patients compared with healthy controls during OKS (Dieterich et al. 2007).

The OKN is modulated by attention: OKN gain increases if the peripheral motion is the focus of covert attention while fixating on the center of the visual scene (Kanari et al. 2017; Williams et al. 2016; Rubinstein and Abel 2011). Transcranial magnetic stimulation (TMS) to the rFEF can affect smooth pursuit eye movements (Nuding et al. 2009; Drew and van Donkelaar 2007; Gagnon 2006). FEF TMS can not only delay eye movements, but also facilitate perception, as if similar to the effects of covert attention: a single pulse of TMS delivered over the right FEF shortly before target onset increases visual perceptual sensitivity at detection tasks (Grosbras and Paus 2003; Chanes et al. 2012). Given then that the OKN can be modulated by attention, and that attentional selection can be influenced by FEF TMS, and that the FEF is activated during OKN, this study asks how any role of FEF during OKS can be related to its oculomotor and/or visual perceptual functions.

Hence the aim of the current study was to dissociate any causal roles of the right FEF in OKS, OKN and the perceptual consequences thereof. The hypothesis was that right FEF TMS plays a driving role in maintaining motion discrimination during OKN, through compensating for the perceptual consequences of those eye movements. Single-pulse TMS was applied over the right FEF (or over a right M1 control site) shortly before a target was presented, during a visual motion discrimination task under OKS. FEF TMS delivered 33 ms before still target onset was expected to increase the perceptual sensitivity in the motion discrimination task; higher performance (lower error rates) was predicted, compensating for the continuous eye movements induced by the OKS. A lesser or different TMS effect was expected in the control task in which the eyes were fixating centrally on a dot superimposed upon the moving background. Eye movements were recorded to investigate whether the TMS was also modulating the oculomotor control function of the FEF during the OKN blocks, and if the perturbation of the optokinetic response was associated with the visual perceptual change. In the control task, unconfounded by eye movements, brain activity was measured with electroencephalography (EEG) to identify the neural correlate of the task (motion discrimination) and any TMS modulation.

Materials and Methods

Participants

16 healthy volunteers (mean age 28 ± 5 years, 8 female) participated in Experiment 1 and a different 16 (mean age 27 ± 5 years, 8 female) took part in the control Experiment 2. All were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971) with no prior history of neurological or psychiatric disorder, and normal or corrected-to-normal vision. Each participant gave informed consent, completing a TMS safety screening questionnaire (Rossi et al. 2009) for a protocol approved by the LMU Munich Medical faculty ethics committee. Participants were compensated for participation, either with 10 euros per hour or course credit.

Procedure

The perceptual consequences of a reflexive eye movement were investigated using Optokinetic Nystagmus (OKN). OKN was elicited by a moving visual stimulus of vertical black and grey bars (Optokinetic Stimulation, OKS). In order to investigate the perceptual consequences of OKN, dots were presented simultaneously with OKS. The dots were introduced to provide a measure of motion discrimination during, or despite, optokinetic stimulation i.e. in the context of additional motion of the background visual scene. The perception of the dots was measured during OKN and also during separate Fixation blocks in which the participants were required to fixate on an additional cross located in the center of the moving background. Six OKN blocks and six Fixation blocks were presented in a randomized order. A total of twelve 5 min blocks of 60 trials was performed by the participants. Each block was preceded by eyetracker calibration (approx. 10 s). The same experimental procedure was performed in the Experiment 1 and 2. Subjects received 10 min training before testing.

Participants completed a debriefing questionnaire at the end of the experimental session to check that the two experiments did not differ in terms of overall experience, rated from 0-100: whether they suffered from motion sickness or self-motion during the experiment (or in general), perceived difficulty of fixating on a moving background or of the perceived eye movements during OKS. No difference was observed between the two experiments in any the reported responses (p's > 0.05).

Stimuli

Participants discriminated the direction of briefly moving dots presented on an optokinetic background of moving bars (see Fig. 1). The stimuli were presented 40 cm from the participant on a LCD monitor (1680 x 1050 pixel resolution) with a refresh rate of 60 Hz. The participant's head was stabilized on a chin-rest such that their eyes were level with the center of the screen. The edges of the screen were covered by a black rectangular paper frame. The background was 48° wide and 24° tall (diameter in degrees of visual angle) composed of 19 black (RGB: 0, 0, 0) and 19 grey (RGB: 105, 105, 105) bars. Bars moved leftward at 33°/s(bar width 2.3 cm/3.3° VA: note that previous studies have showed no differences in

OKN elicited by leftward or rightward moving stimuli (Konen et al. 2005; Dieterich et al. 2007). The selection of the right FEF accordingly led us to the use of contralateral OKS (leftward motion). Previous studies showed no difference in the eye velocity induced by left or right optokinetic stimulation (e.g. Konen et al. 2005, Dieterich et al. 2007). OKN velocity here was faster than in some previous studies (8-10°/s): differences in optokinetic response between vestibular patients and healthy controls became clearer at higher velocity (Zee et al. 1976). White dots (1.6 cm-diameter, RGB: 255, 255, 255) were presented for 100 ms in either the upper or lower part of the screen with equal probability (and at 15° eccentricity). The background speed was kept constant whereas each dot moved at a speed between 1 to 32°/s: background and the dots never moved at the same speed. The dot speeds were randomly and uniformly distributed between 1 and 32°/s in steps of 1°/s. Dot location, direction and speed were randomized. Three types of dots were presented with equal probability: leftward-dots, still-dots and rightwards-dots. Participants were required to respond as quickly and as accurately as possible to the direction of stimulus motion by button press, (leftward, still or rightward with the index, third or fourth finger respectively) while looking passively at the middle of the screen (OKN-Block) or while they were fixating on a cross located in the middle of the moving background (Fixation-Block). Responses were registered via button presses with a response box using their right hand. On Fixation blocks only, a black fixation cross was drawn in a grey dot (1.6 cm diameter, RGB: 128, 128, 128) to prevent from perceiving it as moving with the background.

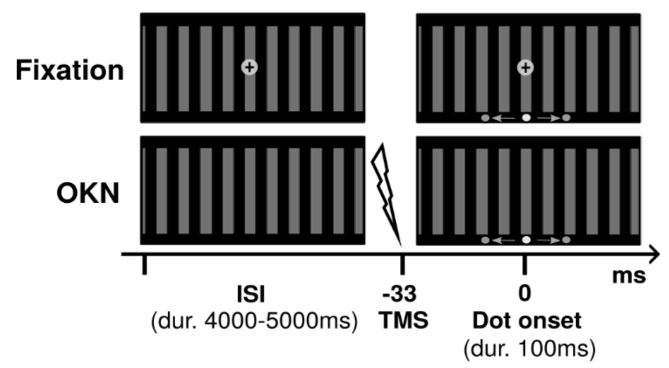


Fig. 1 *Visual motion discrimination task during optokinetic stimulation. Throughout both blocks, Fixation (first row) and OKN (second row), bars were moving to the left at 33°/s and visual target stimuli (dots) were presented in either the upper or lower part of the screen. Dots moved left, right or still and the inter stimulus interval (ISI) between dot onset ranged from 4000 to 5000 ms. A single TMS pulse was delivered 33ms before dot onset in 50% of the trials. Participants discriminated whether the dot was moving left, right or was still by pressing a button. On Fixation blocks an additional central fixation point allowed the participants to fixate and not make eye movements.*

TMS

A single-pulse of TMS preceded half of the trials. Experiment 1 investigated the causal role of the right Frontal Eye Field (rFEF) in visual motion discrimination during OKS. The FEF in the right hemisphere was defined anatomically based on individual 3T structural MRI scans as immediately anterior to the intersection of the inferior part of the superior precentral sulcus and the superior frontal sulcus (Paus 1996). The target site was marked on each participant's structural MRI scan using infrared stereotactic registration (Brainsight, Rogue Research, Canada) and converted into MNI space (mean MNI coordinates x= 34 ± 4, y= 5 ±

6, z= 56 ± 4, see Fig. 2). Experiment 2 was a control experiment exploring the effect of TMS over the right primary motor cortex (rM1), determined individually as the site where TMS elicited a selective finger twitch. The rM1 site was then marked on fifteen participants' MRI scan (scans were available for 15 of 16 participants) and converted into MNI space (mean MNI coordinates x= 34 ± 5, y= -17 ± 11, z= 54 ± 10, see Fig. 2). A clear overlap on the precentral gyrus between the two groups is visible in Figure 2; the more posterior dark grey spot indicates two individual TMS sites showing a complete overlap between one rFEF target location and one rM1. Single-pulse TMS was applied (MagPro X100, Magventure, Denmark) with a figure-of-eight coil (MCF-B70, outer winding diameter: 97mm) on half of trials. TMS was applied shortly before dot onset (33 ms) as the theoretically optimal time to stimulate FEF between TMS and target presentation (Neggers et al. 2007) based on the estimated difference between transmission time from the FEF to the visual cortex (c.100 ms) and from the retina to the cortex (c.66 ms). The TMS pulse was delivered with an intensity of 90% of the individual passive motor threshold (mean intensity: 45.5 ± 2% (rFEF) and 42 ± 1.5% (rM1) of maximal stimulator output). Subthreshold TMS was used to prevent any distraction by motor twitches in the M1 control group (Franza et al., 2019). Although several FEF-TMS studies in the literature used suprathreshold TMS, some others used a fixed percentage of maximal stimulator output of the machines independently from individual MT (Silvanto et al. 2006, Muggleton et al. 2003, O’Shea et al. 2004). Additionally, lower intensities minimize TMS artefacts in the EEG signal (Ilmoniemi and Kicić, 2010). In order to prevent the TMS coil from touching the EEG electrodes, foam bridges 1 cm high were glued to the cap surrounding the target site. Since the efficacy of TMS decreases with distance, the motor threshold was also determined with the bridge in place. To ensure that the non-specific artifact of TMS (the sound and feel) were controlled for, the same intensity of stimulation was used in both groups. In addition, we checked that there were no marked differences in the distance between the TMS coil and the cortical surface between the two groups using the neuronavigation data: scalp-cortex and coil-cortex distances were variable between participants but did not differ between groups, indicating that the effective TMS was comparable between FEF and M1 experiments (distance in mm: coil-to-cortex 22.3 ± 5.5, [range,14.7-33.0] (rFEF) and 24.1 ± 5.1, [range, 13.6-32.7] (rM1); scalp-to-cortex 13.8 ± 2.4, [range, 10.4-17.7] (rFEF) and 13.6 ± 2.9, [range, 7.6-17.8] (rM1); no significant differences between the two groups in coil-to-cortex distance (t(30) = -.95, P = 0.35) or scalp-to-cortex distance (t(30) = -.24, P = 0.8). Although another approach would have been to adjust the TMS intensity according to distance between the TMS coil and the targeted region of interest, this was not necessarily more optimal than the method used in our specific experiment in which we do not know a priori the depth of the key region within the FEF that is causally necessary. The TMS coil was held with the handle pointing backwards in the group of participants that received rFEF-TMS as in previous studies (O'Shea et al. 2004; Taylor et al. 2011). In the group that received rM1-TMS the coil was held by the experimenter with the handle pointing rightwards which eliminated the possibility of any TMS-elicited twitches in the contralateral hand, and this was checked before each experimental session. Participants wore ear plugs throughout as recommended by guidelines due to hearing safety concerns (Rossi et al. 2009). An alternative approach is to use auditory masking to minimize the auditory ERP in the TMS evoked potential (e.g. Gosseries et al., 2015). We chose not to use that in this particular experiment in case the loud ongoing noise from by the mask would distract attention from the ongoing optokinetic nystagmus and task: it is as yet unclear whether optokinetic stimulation interacts with auditory masking. Importantly, in both rFEF and control site groups participants were exposed to TMS pulses with the same volume because TMS intensity was identical throughout, meaning that any sensory ERP components from the TMS non-specific artifact are controlled for in this design.

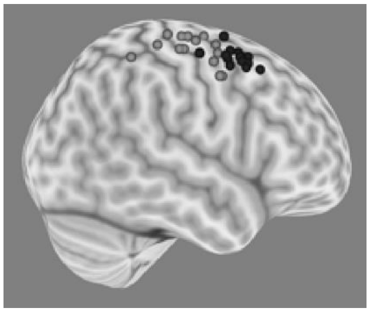


Fig.2 *Location of individual right FEF (in dark grey) and right M1 (in grey) overlaid on a 3D reconstruction of template 152-MNI brain (peeling depth: 8 mm). Spatial spread of both sites in MNI space is in line with previous work (see Mayka et al. 2006; Paus et al. 1996).*

Event Related Potential Recording

EEG data from the fixation block (i.e. without eye movement artifacts) was analyzed. EEG was recorded continuously at 1000 Hz (BrainAmp DC amplifier, Brain Products, Munich, Germany) from 59 scalp sites using passive Ag/AgCl electrodes placed according to the 10-10 international system (AEEGS 1991). No online filters were applied. Additional electrodes were used for ground (between FPz and Fz), reference (ear lobes, active reference positioned on the left) and electrooculography (EOG electrodes were placed below and lateral to each eye). The impedance was kept below 10 KΩ for all electrodes. Data analyses were performed in MATLAB (MathWorks, Natick MA) using customized scripts and the EEGLAB Toolbox (Delorme and Makeig 2004). The EEG signals were re-referenced offline to the average of the left and right ear lobes. The signal from below the left eye was re-referenced to FP1 to form a vertical EOG and the left EOG was re-referenced to the right EOG to form a horizontal

EOG. Due to TMS artifacts a linear interpolation was applied from 5 ms before to 45 ms after each pulse. Following EEG data were low-pass filtered at 30 Hz with a Butterworth filter (18 dB/octave) (Luck 2014). Following pre-processing, ERPs were created from epoch starting 100 ms before and ending 399 ms after dot onset. The signal was baseline corrected to the 100 ms before dot onset. Epochs were rejected if the peak-to-peak EEG signal exceeded ± 100 μV in any channels or if the vertical and horizontal EOGs exceeded ± 80 μV (Sawaki et al. 2015). A minimum number of 30 trials per condition had been established as the criterion to maintain data quality but no channels had to be excluded. Upper and lower visual field stimuli were combined, giving 60 trials per condition. The main ERP analysis aimed to find at which EEG electrodes and time bins any effect of FEF TMS was statistically significant. To reduce the risk of false-positives through multiple comparisons (Luck and Gaspelin 2017) we used a region of interest (ROI) approach. First we formed a ROI using no-TMS data to find the electrodes and time bins at which our task itself had a maximal effect. Secondly we tested for the effect of task without TMS. Thirdly, the main analysis then tested for TMS effects on how task modulated activity within that ROI. In the first step, to form the ROI from all channels were the mean signal amplitude difference between left dot-motion and right dot-motion trials was compared. Still dot trials were not included to form the ROI due to the large widespread ERP activity produced by any motion versus static displays. Six right frontal electrodes (F2, F4, FC2, FC4, C2 and C4) presented the greatest amplitude difference (> 1 μV) in the 240- to 300 ms time bin after dot onset and therefore a region of interest (ROI) was defined as the mean amplitude from these six electrodes. In the second step, the task effect on the ROI ERPs was tested using repeated measures analysis of variance. One way ANOVA on condition as factor (left vs still vs right) was conducted. In the third step, in order to determine how the rFEF was critical for decreasing visual acuity of leftward-moving dot targets, the effect of TMS upon the ERPs during the visual motion discrimination task was also measured. The factors tested were condition (left vs still vs right) and TMS (yes vs no).

Time-Frequency Analysis

The temporal dynamics of induced oscillations were investigated by the Short-Time Fourier transform (STFT) method (Cohen 2014). Brain oscillation changes were examined on visual targets with and without TMS. We used a segment of the data, comprising 300 ms before and 300 ms after dot onset. The segments were multiplied with a Hanning tapered sliding time window (300ms) in steps of 20 ms. These parameters resulted in a 90% overlap between successive time segments. The power was extracted for the alpha frequency range from 8 Hz to 12 Hz (shown up to 40 Hz in the figures), in all subjects and for every condition, TMS and no-TMS trials. The output was normalized to the baseline period (pre-stimulus interval, -300 ms to-0 ms). The same parameters for TMS artifact and epochs rejection used for the ERPs pre-processing were applied to create the time segments for STFT (see "Event Related Potential Recording"). A central right frontal ROI (Fz, F2, FC2) and a central posterior ROI (O1, OZ, O2) presented the biggest alpha power difference between task conditions. Stimulus-induced oscillations were also analyzed, for no-TMS and TMS trials, in the alpha range for the frontal and posterior ROI.

Eye movement recording

Eye movements were recorded by head-mounted video-oculography of the left eye with a sampling rate of 220 Hz (EyeSeeCam system, EyeSeeTec, Munich). Offline data analysis used MATLAB. Blinks were removed. Quick phases were defined as when eye velocity was greater than 10 °/s and the absolute acceleration was greater than 300 $°/s^2$. The start point and the end point of the QPs were determined from the time of peak velocity to the time when the eye velocity values were close to 0°/s (eye changed direction). A customized code was developed to calculate the mean of slow phases (SPs) nystagmus. Eye movement data were segmented for the analysis and task and TMS effect were investigated during the 300 ms before and after the TMS pulse. On TMS trials, the pulse was always delivered 33 ms before dot onset, and so 33 ms preceding dot onset was also established as time zero for no-TMS trials. The length of the segments was based on reaction time (RT) results in order to avoid potential contamination in the eye movement signal from actual movement of the finger; no responses (finger movements) faster than 300 ms were recorded. Our design addressed the slow phase of the nystagmus, used in previous studies to evaluate optokinetic responses (Dieterich et al. 2007, Konen et al. 2005) and to investigate attentional effects during optokinetic stimulation (Kanari et al. 2017). Note however that TMS was triggered independently of ongoing saccades. We can estimate how often TMS was applied during the fast phase, based on the mean length of slow and fast phases of nystagmus in our data. The relative duration of time spent during the quick phases was calculated separately for rFEF and rM1 group, as respectively 13.7% and 13.6% (i.e. with high similarity between rFEF and M1 groups). It is however unknown exactly at which time FEF TMS affects visual processing relative to the TMS pulse: it may be that the effects of FEF TMS spread to other brain areas and a key effect is essentially occurring distally (Ruff et al. 2006, Taylor et al. 2007, Silvanto et al. 2007). This logic is also used to dictate FEF TMS timing (Neggers et al. 2007). However due to the absence of being able to measure this directly it was not possible to exclude trials where the effect of the application of the FEF TMS was simultaneous with the quick phase. Quick phases are however so fast (and saccade-like) that no visual discrimination is possible during the eye movement (Campbell and Wurtz, 1978, Bridgeman, 2011) and therefore we did not predict any tractable perception nor any contribution from a TMS effect on perception during those eye movements.

Results

In the following section are described the findings of the two Experiments. Experiment 1 investigated the causal role of the right FEF in dealing with the perceptual consequences of reflexive eye movements. In the Experiment 2, the TMS was delivered over the control site, rM1; the visual motion discrimination task was identical in the two Experiments. It has to be noted that two different groups of participants took part in the two Experiments; this decision was made in order to reduce the intra-individual variability between experimental sessions.

Behavioral effect of TMS

Experiment 1: right FEF

A behavioral analysis tested whether dot direction discrimination accuracy (left, still, right) was modulated by rFEF TMS. The analysis was performed in OKN and Fixation blocks separately. rFEF TMS modulated the visual motion discrimination task differently when participants were moving their eyes in response to the moving background (OKN block) or were fixating while the background moved (Fixation block).

There was main effect of task direction in OKN and Fixation blocks ($F(2,30) = 12,26$, $P < 0.001$; $F(2,30) = 24,79$, $P < 0.001$, respectively). TMS had different effect depending on which direction the dot was moving, the interaction between condition (left vs still vs right) and TMS (yes vs no) was present in both blocks (OKN: $F(2,30) = 8.09$, $P < 0.01$; Fixation:

$F(2,30) = 5.56$, $P < 0.05$). This effect was driven by rFEF TMS increasing accuracy when the dot was still during OKN ($t(15) = -3.51$, $P < 0.01$) and decreasing accuracy for left dot-motion trials ($t(15) = 2.38$, $P < 0.05$) during Fixation, relative to no-TMS (see Fig. 3, panel A). These effects can also be observed at individual level, in twelve and thirteen out of sixteen participants, respectively for Fixation or OKN (see Fig. 3, panel C). FEF TMS therefore increased the likelihood of a correct “still” report on still trials and decreased the probability of a correct “left” report on left dot-motion trials. This effect was specific to accuracy and not reaction times (RTs); although there were main effects of TMS and dot direction on RTs in OKN block ($F(1,15) = 9.16$, $P < 0.01$; $F(2,30) = 4.09$, $P < 0.05$, respectively) and in Fixation block ($F(1,15) = 14.26$, $P < 0.01$; $F(2,30) = 5.35$, $P < 0.05$, respectively). Reaction times were faster following stimulation of the right FEF compared to baseline, during Fixation and OKN blocks, in the range of 27-41 ms (see Tab. 1, C and D for details) but no direction-specific TMS effect was found ($P > 0.1$). A further analysis was performed to test for a gender effect in the visual motion discrimination task, with no significant differences were reported between females and males (all p’s > 0.2).

As mentioned in the Methods section, the dots were moving at different speeds. A median split was used to separate individual accuracy data into two subgroups, slower versus faster speed. Better performance, as expected, was registered when dots were moving at faster than slower speed, independently from dot direction (left vs right) or TMS (yes vs no) (all P’s $<$ .0001).

Experiment 2: right M1

Experiment 2 confirmed the specificity of the causal role of rFEF in improving task performance in OKN blocks and impairing performance in Fixation blocks, by demonstrating that none of these effects were observed when TMS was delivered over the control site, rM1. TMS over rM1 did not modulate the visual motion discrimination task in OKN nor in Fixation blocks (see Fig.3, panel B). rM1 stimulation did also not change performance in terms of accuracy: analysis of blocks separately showed that TMS had no impact on the task (F(2,30) = 1.38, P > 0.2, OKN and F(2,30) = 0.36, P > 0.6, Fixation). A main effect of task was present in both blocks, OKN and Fixation (F(2,30) = 4.54, P = 0.02, F(2,30) = 25.14, P < 0.001, respectively). Any TMS effect was also explored in RT data; as with FEF. In experiment 2, faster responses, in the range of 19-34 ms were elicited after TMS compared to baseline (see Tab. 1,G and H for details) but no interaction was found between dot direction and TMS (F(2,30) = 1.52, P > 0.2, Fixation and F(2,30) = 1.22, P > 0.3, OKN); main effects of task were observed in OKN and Fixation blocks (F(2,30) = 3.36, P < 0.05 and F(2,30) = 4.04, P < 0.05, respectively) and a main effect of TMS was present in Fixation blocks (F(1,15) = 20.64, P < 0.001). In Experiment 2 the lack of gender effect and the effect of dot speeds on the visual motion discrimination task were confirmed (see "Experiment 1: right FEF").

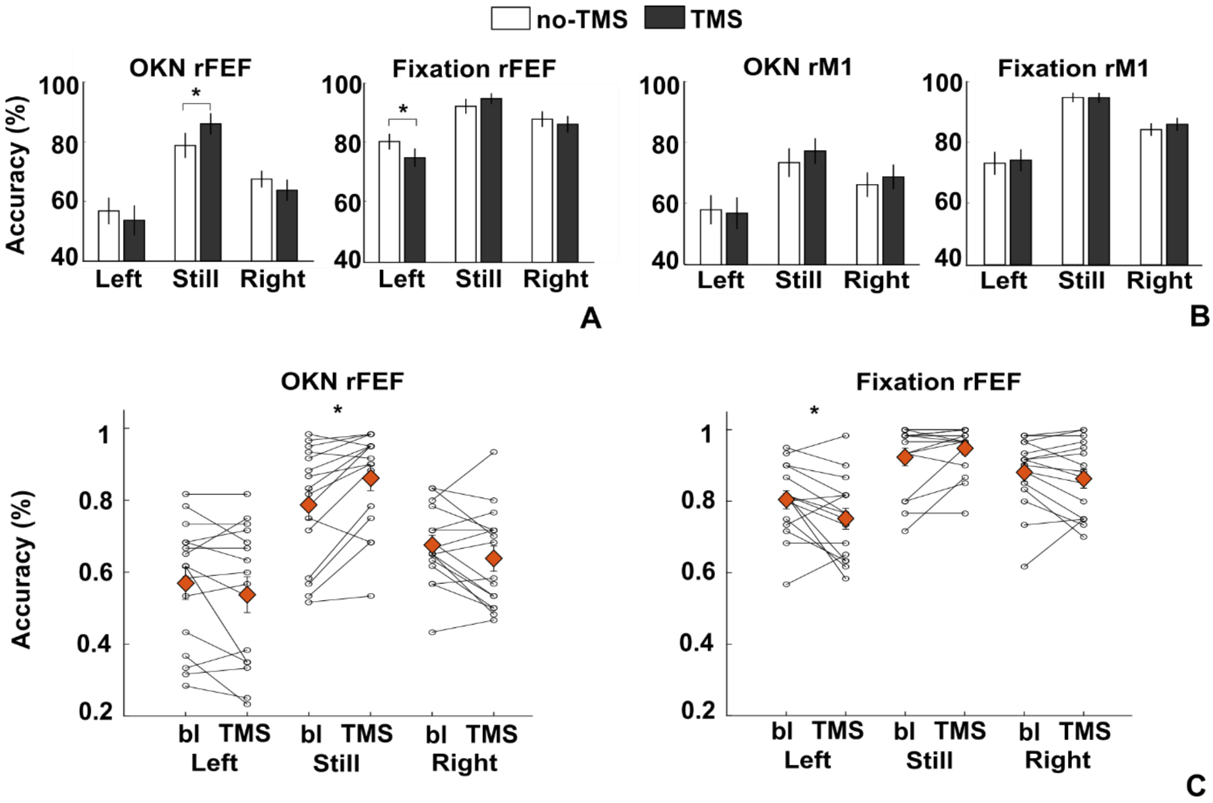


Fig. 3: *rFEF TMS increased the accuracy for still dots during OKN (left side, panel A) and decreased the accuracy for leftward moving dots during Fixation (right side, panel A). No significant additional TMS effect was found. rM1 TMS did not affect the visual motion discrimination task significantly, in OKN or fixation block (panel B). Blank bars indicate no-TMS data and grey bars represent TMS data for leftward, still and rightward dots. Error bars show standard error from the mean in all figures. Individual data (empty circles) and mean (diamonds) for accuracy data in rFEF group (panel C). Data per each dot direction are presented, at baseline (bl) and following FEF stimulation (TMS). The task specific TMS effects found in leftward dot trials for Fixation, and in still dot trials for OKN were reported in the majority of participants.*

Event-related potentials during Fixation

Experiment 1: right FEF

The behavioral analysis above demonstrated that TMS affected performance on the dot direction discrimination task, during OKN and Fixation. Next we looked at brain activity during Fixation blocks. To see if TMS was affecting neural activity in a way similar to the task manipulation, an initial analysis defined at which times and from which electrodes the effect of the task (without TMS) on the ERP was maximal, and then a subsequent analysis focused on whether TMS affected this effect (akin to a region of interest analysis, and one approach to tackle the multiple comparison problem with event related potentials, see Luck and Gaspelin 2017). The task effect was explored on no-TMS trials as the difference between waveforms from leftward and rightward moving stimuli. The largest differences (> 1µV) occurred at right frontal-central electrodes for the 240- to 300 ms time bin which were therefore included in the region of interest (ROI): F2, F4, FC2, FC4, C2, and C4 (see Fig. 4 A).

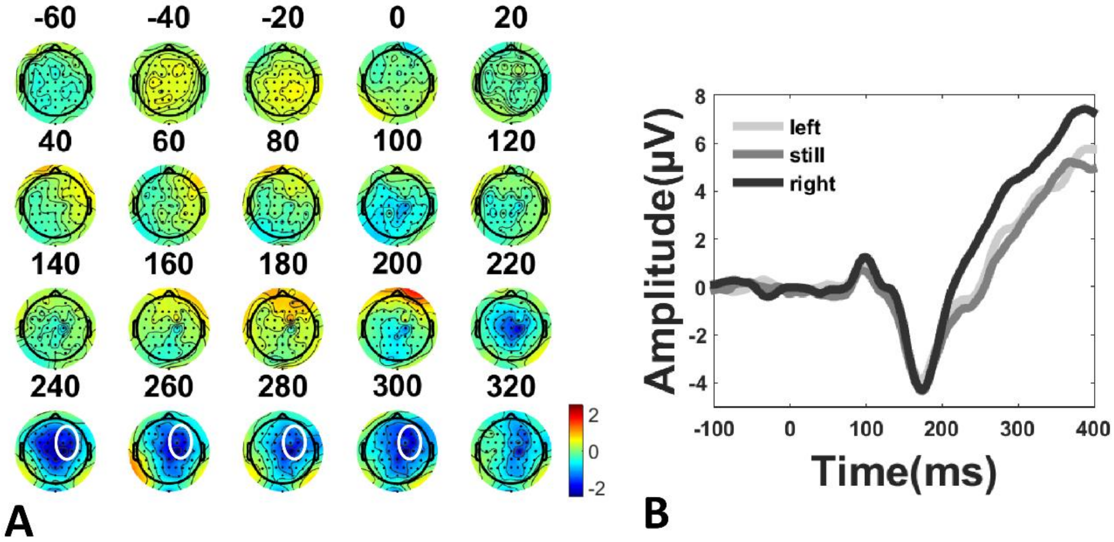


Fig. 4 *Task effect.* ***A.*** *Topographies of task effect without TMS, used to select electrodes and time-bins for the main analysis on the TMS data. Scalp topographies show mean differences (in 20 ms windows) between the ERPS evoked by leftward- and rightward moving-dots. Strongest task effects are 240- to 300 ms over right-frontal electrodes (marked with white circles).* ***B.*** *ERP Waveforms of task effect without TMS. A larger late positivity in the right frontal ROI was elicited by rightward moving dots (dark grey) than leftward moving (light grey) and still dots (grey). Visual dot stimulus was presented at time zero.*

As expected, within this ROI a statistically significant effect of task was evident ($F(2,30) = 9.40$, $P = 0.001$). Specifically, rightward moving dots elicited a larger (more positive) late component than leftward moving dots and still dots ($t(15) = -4.40$, $P < 0.01$; $t(15) = -4.14$, $P < 0.01$, respectively) (see, Fig. 4, B).

Having derived the optimal measure of how our task affected neural activity without TMS we were then able to use this to guide the TMS analysis without needing to test over all electrodes and time-bins and therefore reducing the multiple comparisons problem (Luck and Gaspelin 2017). The time window identified for the ERP analysis, starting 240 ms after dot onset, was far enough from the TMS pulse (which was 33 ms preceding the dot i.e. 273 ms beforehand) that any effects cannot be due to the initial TMS artifact, which lasts less than 40/50 ms (e.g. Taylor et al. 2008) and which furthermore would be equivalent in FEF and M1 groups. Although faster sampling rates of recording (e.g. 5000Hz rather than 1000 Hz) can capture the initial sub-millisecond spike of the TMS pulse (Veniero et al. 2009), we were interested in events substantially later, namely the visual-evoked potential from the dot targets. The effect of rFEF TMS ERP was investigated following the same ANOVA design as used for behavioral data. Importantly, a direction-specific TMS effect in the behavioral results was also present in this late right frontal-central ERPs ($F(2,30) = 4.18$, $P < 0.05$): the single pulse TMS delivered 33ms before the dot onset boosted the frontal ROI response, and this was present for leftward moving dots and for still dots, relative to no-TMS ERPs (see, Fig.6, panel A; $t(15) = -3.41$, $P < 0.05$and $t(15) = -2.70$, $P < 0.05$ respectively). rFEF TMS increased the amplitude of late right frontal ERPs consistent with a contribution of the FEF in the late frontal stage of processing which the task also modulated without TMS. This modulation was prominent for dots moving in the same direction as the OKS (leftward), and for still dots. Fig. 7 (panel A) shows the individual difference scores between TMS and no-TMS ERP amplitudes. Note that the pattern of results do not change if the participants showing extreme values were excluded from the analysis, as the participants showing extreme values following TMS also displayed high ERP amplitudes at baseline.

Experiment 2: right M1

Like the task effect observed in Experiment 1, within the right frontal ROI selected, the rightward moving dots elicited a larger late component than leftward moving dots and still dots ($t(15) = -5.13$, $P < 0.0001$, $t(15) = -2.29$, $P < 0.05$, respectively, Fig. 5). No significant difference was found between leftward moving dots and still dots ($t(15) = -1.76$, $P \geq 0.1$). This analysis indicates a comparable response to the visual stimuli at baseline, in both the FEF and M1 groups.

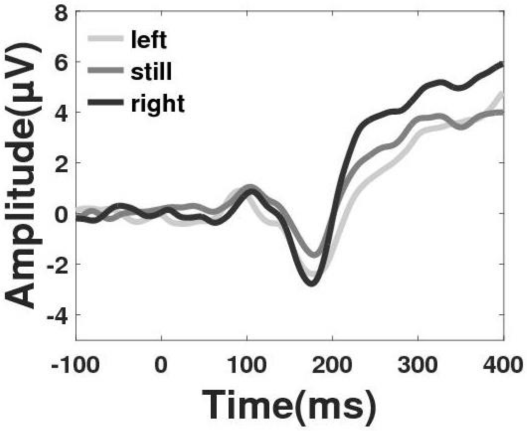


Fig. 5: *ERP Waveforms of task effect without TMS in the Experiment 2. A larger late positivity in the right frontal ROI, at the 240-to 300 ms time bin) was elicited by rightward moving dots (dark grey) than leftward moving (light grey) and still dots (grey). Visual dot stimulus was presented at time zero.*

Unlike the divergence after rFEF TMS, a strong overlap between no-TMS and rM1 TMS waveforms ERPs over the late component (240- to 300 ms time bin) was observed (Fig.6, panel B). Statistical analysis confirmed that no direction specific TMS effect was found in the ERPs, consistent with rM1 not being involved in this frontal stage of visual motion discrimination processing (F(2,30) = 0.83, P > 0.4). In experiment 2, there was then no difference at these electrodes between no-TMS and TMS dot-locked ERPs when TMS was delivered over rM1. Fig. 7 (panel B) shows the individual difference scores between TMS and no-TMS ERP amplitudes. Differences from FEF Experiment 1 cannot be attributed to different distances between TMS coil and EEG electrodes, because such effects did not occur at the electrodes nearest the M1 coil either (see Fig. 8). The variability in right M1 TMS target locations (see Fig.2) and the anatomical proximity between the two stimulated brain areas, confirm the specific causal role of the right FEF in this task.

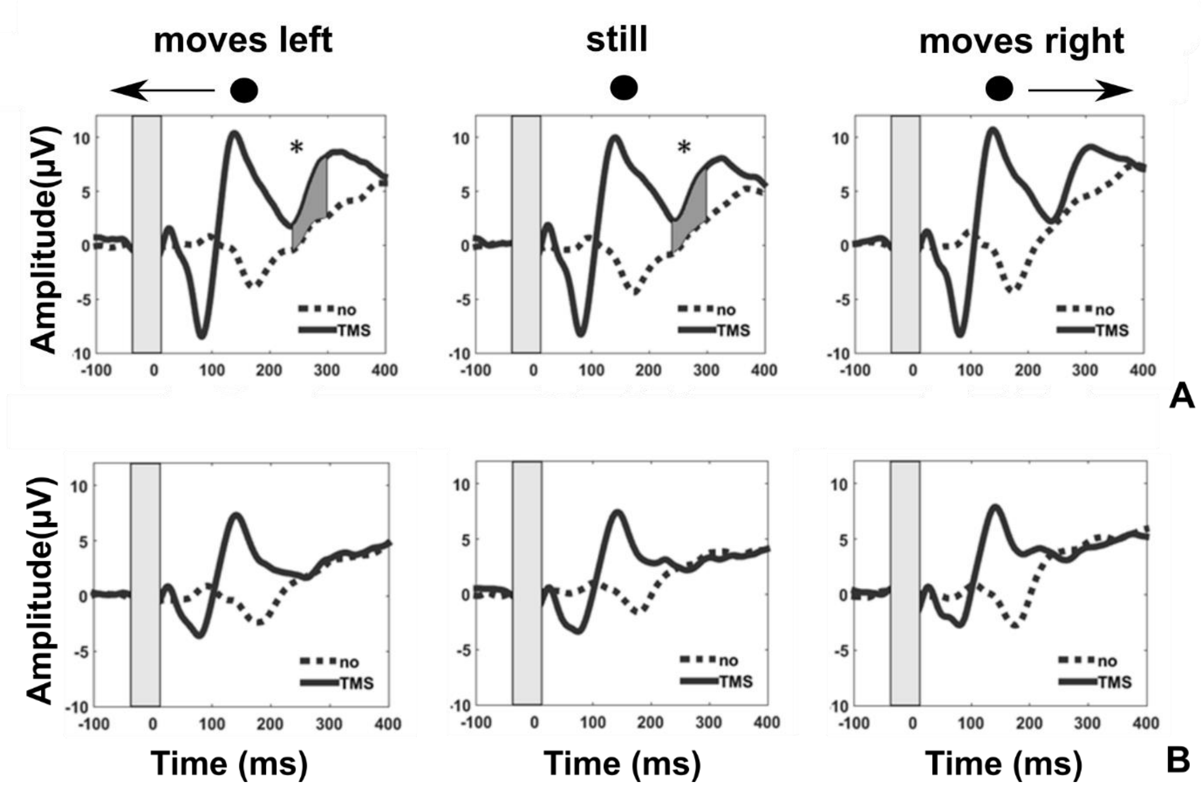


Fig. 6: *Direction specific TMS effect on ERPs data for leftward moving dot and still dot trials from Experiment 1 (panel A). The rFEF-TMS increased the amplitude of the late right frontal ERPs (240- to 300 ms time bin; grey shaded area) which was normally modulated by the task without TMS, implying a contribution of the rFEF in later frontal stages of processing. No effect was observed after rM1 TMS (panel B). Grey shading bars indicate data eliminated because of the TMS pulse artifact. Visual dot stimulus was presented at time zero.*

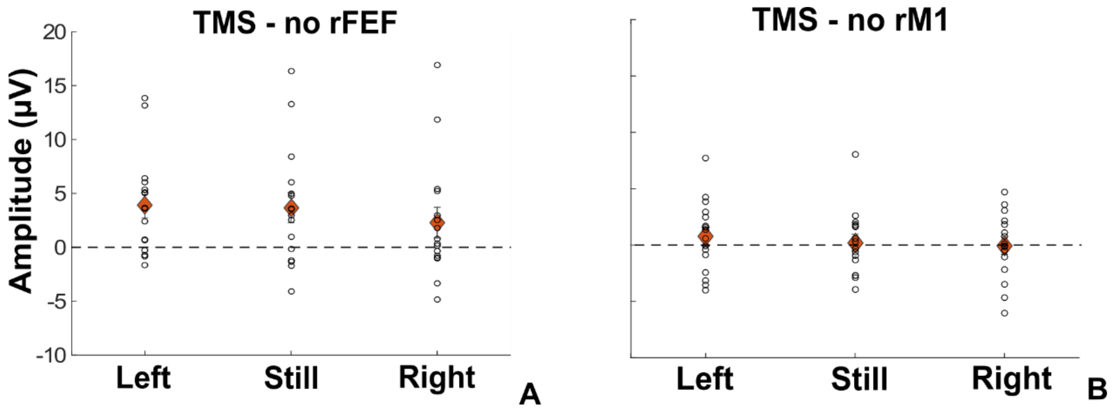
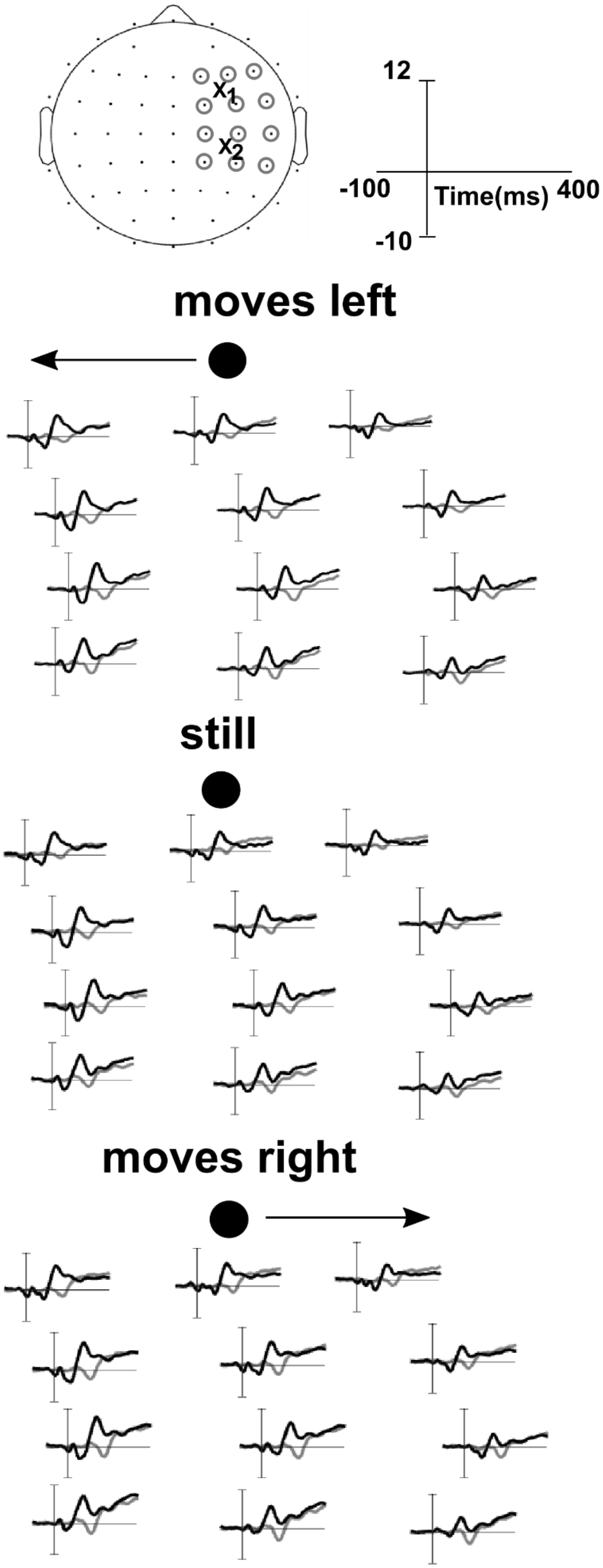


Fig. 7: *Individual ERP amplitude differences between TMS and no-TMS trials (rFEF, panel A and rM1, panel B): each subject is indicated with empty circles for each task direction. Individual data (scatter plot) and mean across participants (diamonds) are superimposed.*



x_1
x_2
12
-100
Time(ms)
400
-10
moves left
still
moves right

Fig. 8: *Differences in effects between FEF (Experiment 1) and control M1 TMS (Experiment 2) cannot be attributed to differences in the distance between TMS coil and EEG electrodes. Figure shows ERPs elicited by rM1 TMS (black line) and no-TMS (grey line) stimuli for each task condition in Experiment 2. Twelve electrodes are shown, marked with grey circles on the channel map location plot (upper panel). The x within "x2" indicates the mean location of the TMS site in the control Experiment 2. Superimposed is the mean location of rFEF TMS site in Experiment 1 ("x1"). The effect of TMS on the ERP shown in Experiment 1 (large positivity from 240-300 ms) is clearly not present on any electrode and so the effects of FEF TMS cannot be ascribed to coil-electrode distance.*

Time-frequency analysis: TMS effect on alpha band oscillations

Experiment 1: right FEF

In the behavioral analysis above, TMS worsened performance during leftward dot-motion trials in Fixation blocks. However, the ERP results showed a pattern of TMS effects that differed, increasing amplitude in the late right frontal ERPs on leftward and still trials. To resolve this we performed a further analysis. There are dynamics in the time-frequency domain of EEG data that are not present in the ERP, and natural oscillatory frequency of cortical systems can be perturbed by direct stimulation (Rosanova et al., 2009). The FEF is a crucial region for perceptual modulation and visuo-spatial attention (Moore and Fallah, 2001; Grosbras and Paus 2002; Ruff et al. 2006; Marshall et al., 2015). Visual discrimination performance is related to alpha power (Hanslmayr et al. 2005) and this can be modulated by TMS (Thut and Miniussi 2009 for review). We hypothesized that if TMS decreased accuracy only when left dot-motion stimuli were presented, a different modulation of alpha band oscillations would occur when TMS was delivered over the rFEF before leftward dot onset compared to when the TMS was delivered before still dots. Previous studies suggested that visual attention can be reflected in posterior alpha that is controlled by the prefrontal cortex (Capotosto et al. 2009; Sauseng et al. 2011). Short-time fast Fourier transform (FFT) was conducted on all electrodes for the three different types of trial. Target-induced alpha power was compared between experimental conditions in the 300 ms window after stimulus onset between 8 and 12 Hz. The alpha power distribution was explored on the double differences between TMS condition (TMS and no-TMS trials) and between dots trials (still minus leftward). In this stage the difference between conditions were investigated in still and leftward dot motion trails in order to identify the neural process underlying visual attention, during fixation on moving background, despite the similarity between these two conditions shown in the ERPs results. Electrodes and time bins showing the greatest difference in alpha power ($> \pm 0.2\ (\mu V)^2$) for two consecutive time windows (300 ms each, see Methods section) were included in the analysis (Cohen, 2014). Differential modulation of alpha power was induced by FEF TMS in left dot-motion and in still dot trials. Strikingly, the topographical power plot of alpha band (Fig. 9, A) showed a clear reduction in alpha power in posterior recording sites (ROI: O1, OZ, O2), and increase in alpha in frontal EEG sites (ROI: FZ, F2, FC2). The greatest difference between conditions was found during the time bin centered on 40- to 60 ms after dot onset. A repeated measure ANOVA was performed to investigate the alpha change in frontal and posterior sites induced by TMS in each dot direction condition. The difference between TMS induced alpha and baseline alpha (TMS − no TMS) in the two ROIs reflects whether alpha modulation (compared to the baseline) occurred in left dot-motion and still trials. Accordingly, a significant interaction was found between factors condition (left vs still vs right) and electrode group (frontal vs posterior) ($F(2,30) = 8.86$, $P < 0.01$) (see Fig. 9, B-C-D). No alpha difference was found between frontal and posterior

ROIs in left dot-motion trials ($t(15) = 0.27$, $P > 0.7$), there were significant differences between sites for still and right dot-motion trials ($t(15) = 3.91$, $P < 0.01$ and $t(15) = 2.20$, $P < 0.05$, respectively). As a consequence of the direction specificity of the TMS effect found, these results cannot be due to non-specific TMS artifacts. Only left dot-motion trials presented a different modulation of alpha power compared to still and right dot-motion trials although the TMS non-specific effects were identical.

A similar alpha power distribution (see Fig. 9-A) was observed in the late time bin, at 260- to 280 ms after dot onset, but without any interaction between condition and electrode group ($P > 0.05$).

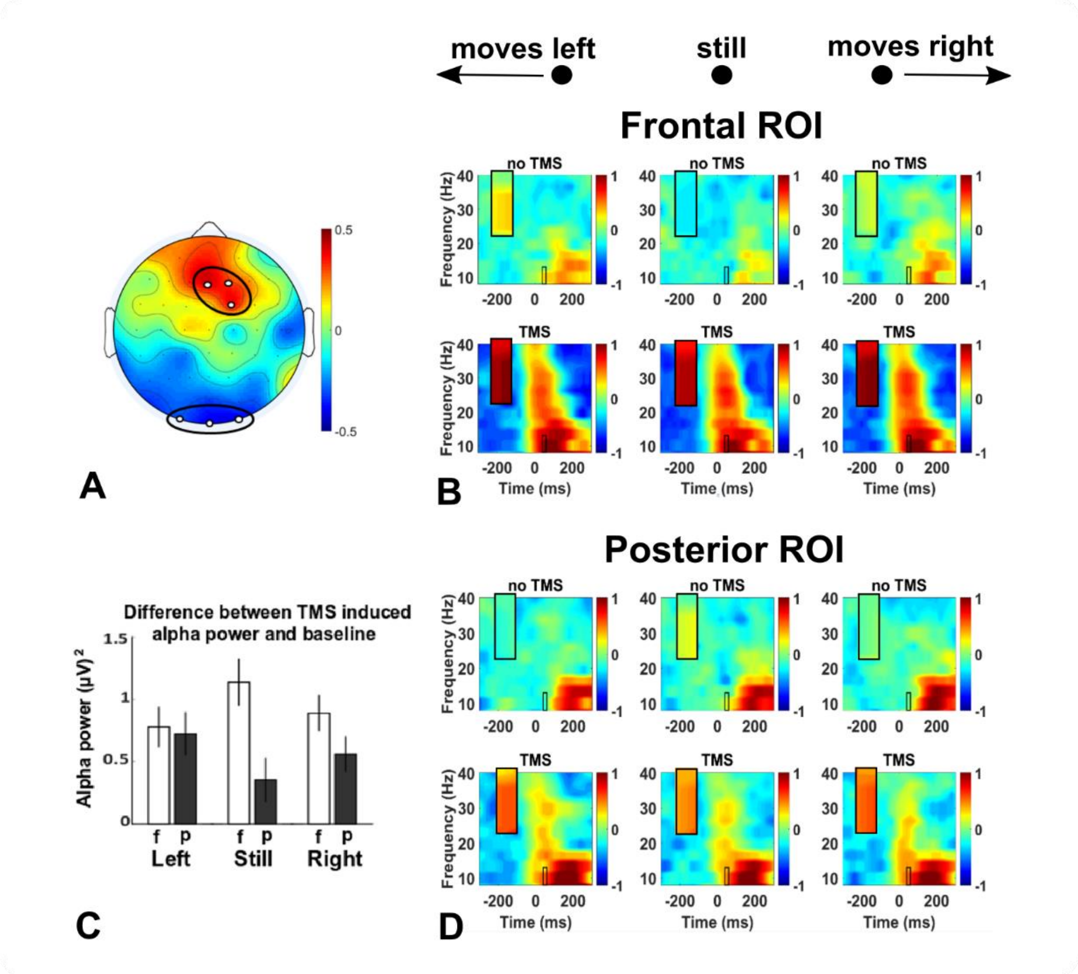


Fig. 9 *FEF TMS disrupts the normal pattern of alpha-band oscillations on leftward dot motion trials* ***A.*** *Topographical map of the mean of alpha power distribution in the double difference between conditions (still minus leftward moving dot trials) and TMS (yes minus no). The map shows the alpha power distribution across the scalp, values were averaged across 40- to 60 ms time bin after dot onset. The largest effects induced by TMS are labeled with a black circle, high alpha in the right central frontal-ROI (FZ, F2, FC2) and low alpha in the central posterior-ROI (O1, OZ, O2). This figure shows that the FEF TMS induced higher alpha oscillation for leftward dot trials than for still dot trials in the posterior site (vice versa for the frontal site).* ***B and D:*** *time-frequency spectra for no-TMS trials (first row) and TMS trials (second row, panel B-D). Scale represents log power from frontal and posterior ROIs. Black rectangle shows alpha power region of interest at 40- to 60 ms time bin after dot onset, expanded as the rectangular inset panels. Dots were presented at time zero, the TMS was delivered 33 ms beforehand.* ***C.*** *Frontal ROI (blank bars) and posterior ROI (grey bars) alpha per each task conditions, showing the TMS effect on alpha relative to the baseline (TMS – no TMS). Each bar represents the subtraction between alpha power changes induced by rFEF TMS (see expanded rectangles, second row in panel A and B) and alpha power at the baseline (see expanded rectangles, first row in panel B and D) extracted from the frontal and posterior ROIs. The alpha changes induced by TMS relative to no-TMS did not show any difference between frontal and posterior sites in left dot motion trials, unlike still and right dot motion trials.*

Experiment 2: right M1

Effects on Alpha oscillations were also tested for in the rM1 group as in Experiment 1, to ensure that the TMS effect observed in Experiment 1 (abolishing the alpha difference between frontal and posterior sites for left dot-motion trials) was rFEF-specific. The results did not show any interaction between dot direction and site, frontal vs posterior ($F(2,30) = 1.82$, $P > 0.1$). There were main effects of task and sites ($F(2,30) = 4.25$, $P\ 0 < 0.05$ and $F(1,15) = 18.44$, $P < 0.01$, respectively). TMS over the control site did not abolish the alpha difference between frontal and posterior sites in left dot-motion trials (see Fig. 10).

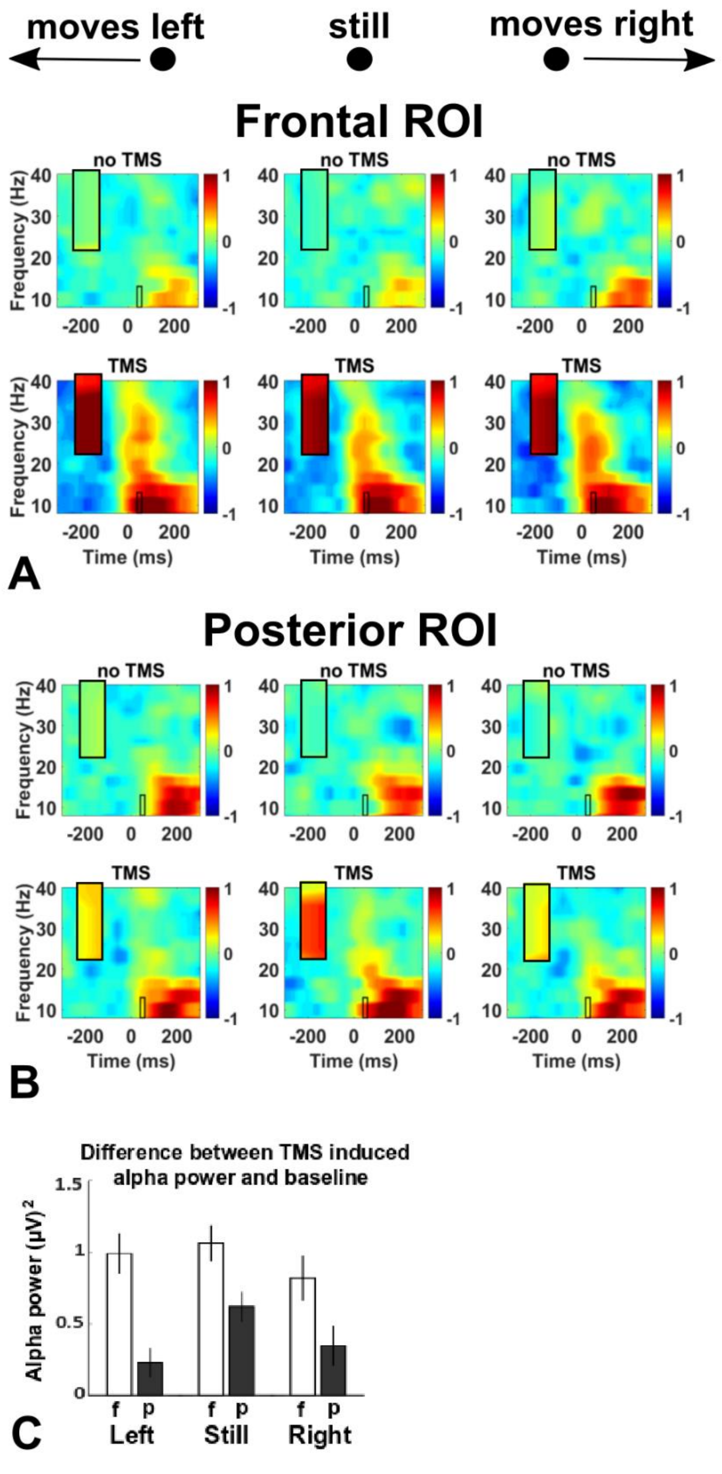


Fig. 10: *Time-frequency spectra for M1 data (Experiment 2).* ***A and B:*** *no-TMS (first row) and TMS trials (second row). Scale represents log power from frontal and posterior ROIs.*

Alpha power in the region of interest at 40- to 60 ms after dot onset is expanded into rectangular inset panels. Dots were presented at time zero, the TMS was delivered 33 ms beforehand. ***C.*** *Frontal ROI (blank bars) and posterior ROI (grey bars) per each task condition, showing the TMS effect on alpha power relative to the baseline (TMS – no TMS). Each bar represents the subtraction between alpha power changes induced by rM1 TMS (see expanded rectangles, second row in panel A and B) and alpha power at the baseline (see expanded rectangles, first row in panel A and B) extracted from the frontal and posterior ROIs. Unlike with FEF TMS, M1 TMS did not abolish the difference between frontal and posterior sites in left dot motion trials.*

Nystagmus slow phase velocity

Experiment 1: right FEF

This analysis examined how the task and TMS modulated nystagmus Slow Phase Velocity (SPV). The difference between post and pre-no-TMS dot/TMS dot SPVs was derived to explore any eye movement speed changes due to the dot itself or due to the stimulation of the rFEF. SPV did not differ between dot direction types when the task modulation was analyzed on no-TMS trials ($F(2,30) = 0.17$, $P \geq 0.8$), showing that the dot, still or moving, did not on its own disrupt the eye movements caused by the OKS. The effect of dot on SPV was also tested against zero to check for potential significant effect of the dot on SPV independent of motion direction, and we did not find any effect (all P’s > 0.05). Changes in SPV between TMS and no-TMS trials were analyzed within condition. The largest SPV difference between post and pre-TMS pulse was found in still-dot trials (see Fig. 11, panel A). The effect of TMS on the SPV was to slow it by 2°/s, from 11°/s (pre pulse) to 9°/s (post pulse), a difference of 19 %. SPV differences, post minus pre no-TMS dot and post minus pre TMS dot, were compared. Only in the still dot task condition did SPV during no-TMS trials differ significantly from SPV in TMS trials (t(15) = 2.88 $P < 0.05$). No significant difference in SPVs between TMS and no-TMS trials was found for leftward and rightward-moving dot trials (P's > 0.9) (see Fig. 11, panel A).

Experiment 2: right M1

As previously described in Experiment 1, the difference between pre and post- no TMS dot/TMS dot SPVs was measured to investigate if any changes in eye movement speed occurred following rM1 TMS. No task effect was found on SPV pre-post differences (F(2,30) = 2.14, $P > 0.1$), meaning as before the dot did not disrupt the OKN. Unlike Experiment 1, this time TMS had no significant effect on the SPV differences for any dot direction (all P's > 0.05) (see Fig. 11, panel B). These results are consistent with previous findings; TMS over M1 did not interfere with smooth pursuit (Mathew et al. 2017).

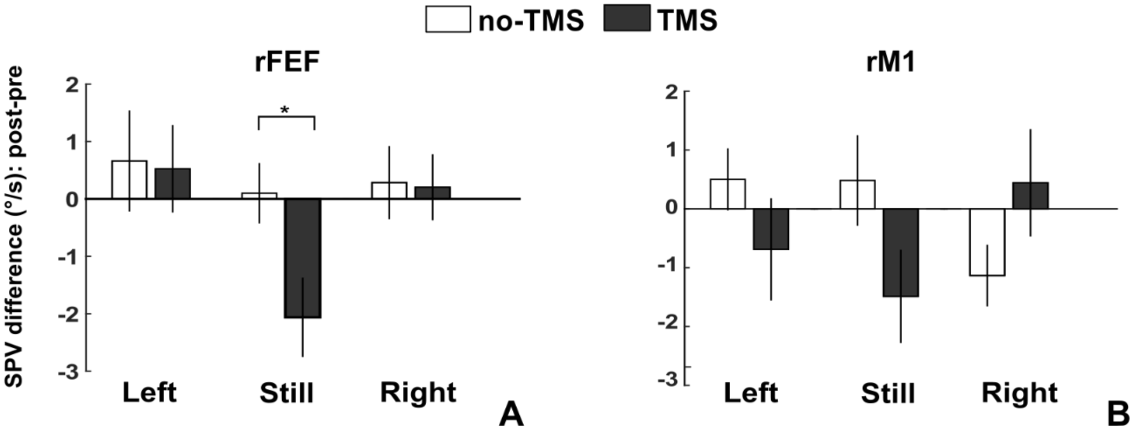


Fig. 11 *rFEF-TMS decreased the Slow Phase Velocity during still dot trials (panel A). Each bar indicates the difference between pre and post target (no-TMS dot/TMS dot) SPVs per dot direction (left, still and right). Blank bars represent no-TMS trials and grey bars show TMS*

trials. Single-pulse rFEF TMS decreased the eye movement speed during still dot trials, but not in leftward and rightward-moving dot trials. Control site did not affect eye movements (panel B).

rFEF vs rM1

A further analysis was performed on the behavioral data to assess the homogeneity of the two groups. An ANOVA with "dot direction" (left vs still vs right) as within-subjects factor and "group" (rFEF vs rM1) as between-subjects factor, for Fixation and OKN blocks, did not reveal any significant interaction between "group" and "dot direction" nor main effect of "group" (F's < 2.9, P's > 0.07). But a main effect of "dot direction" was found for both Fixation and OKN (F's > 9.8, P's < 0.0001: demonstrating that the same task effect was present in the two groups, and so the two groups did not differ on the no-TMS conditions. Furthermore, we also found no difference in slow phase velocity of the OKN at baseline between Exp 1 and Exp 2 (F < 0.96, P > 0.3). In addition, the TMS effect on the visual motion discrimination task was investigated between Experiments 1 and 2. A mixed factorial design with two within-subject factors, dot direction condition (left vs still vs right) and TMS (yes vs no), and one between-subject factor, group (rFEF vs rM1) was used. In the Fixation blocks, a 3-way interaction (task x TMS x group) was found for behavioral and time-frequency data (F(2,60) = 4.13 , P < 0.05; F(2,60) = 8.48, P < 0.01 respectively). The ERP amplitude data showed a 2-way interaction between TMS and group (F(1,30) = 6.09, P < 0.05). In the OKN blocks, the interactions between groups for the behavioral and SPV effect did not reach significance (P > 0.05).These further analyses demonstrate that only rFEF TMS affects visual discrimination performances during moving visual scene, although the repeated measure

ANOVA between groups did not reveal significant interactions when OKN was elicited by the moving visual scene, but only during fixation on the moving background. Importantly, the induced alpha oscillation and the ERPs results draw attention to cortical dynamics following the rFEF perturbation and those are not present after the stimulation of the control site.

A) % Correct Fixation rFEF

	no TMS	TMS		*F*	*P*
Left	0.80	0.75	**Dot direction**	24.79	< .0001
Still	0.92	0.95	**TMS**	1.74	0.21
Right	0.88	0.86	**Dot direction x TMS**	5.56	0.01

B) % Correct OKN rFEF

	no TMS	TMS		*F*	*P*
Left	0.57	0.54	**Dot direction**	12.26	< .0001
Still	0.79	0.86	**TMS**	0.01	0.92
Right	0.68	0.64	**Dot direction x TMS**	8.09	0.002

C) RT Fixation rFEF

	no TMS	TMS		*F*	*P*
Left	684	667	**Dot direction**	5.35	0.012
Still	648	617	**TMS**	14.26	0.002
Right	708	674	**Dot direction x TMS**	1.86	0.18

D) RT OKN rFEF

	no TMS	TMS		*F*	*P*
Left	843	789	**Dot direction**	4.08	0.04
Still	745	693	**TMS**	9.16	0.009
Right	762	745	**Dot direction x TMS**	1.41	0.26

E) % Correct Fixation rM1

	no TMS	TMS		*F*	*P*
Left	0.73	0.74	**Dot direction**	25.14	< .0001
Still	0.95	0.94	**TMS**	9.16	0.482
Right	0.84	0.86	**Dot direction x TMS**	1.41	0.696

F) % Correct OKN rM1

	no TMS	TMS		*F*	*P*
Left	0.58	0.57	**Dot direction**	4.54	0.19
Still	0.74	0.77	**TMS**	3.65	0.076
Right	0.66	0.69	**Dot direction x TMS**	1.38	0.269

G) RT Fixation rM1

	no TMS	TMS		*F*	*P*
Left	727	682	**Dot direction**	4.04	0.033
Still	671	630	**TMS**	20.64	< .0001
Right	683	665	**Dot direction x TMS**	1.52	0.238

H) RT OKN rM1

	no TMS	TMS		*F*	*P*
Left	770	771	**Dot direction**	3.36	0.048
Still	720	685	**TMS**	2.30	0.15
Right	776	755	**Dot direction x TMS**	1.22	0.304

Tab. 1: Behavioral results of Experiment 1 and 2. *The left panel shows the mean percent of correct responses and the mean of the reaction time (RT, given in ms) during Fixation and OKN blocks, at baseline (no TMS) and with stimulation (TMS). The table presents the finding of the group of participants that received TMS over the rFEF, Experiment 1 (A-B-C-D) and*

of the group that received control site TMS, Experiment 2 (rM1, E-F-G-H). The right panel shows the main effects and interactions after repeated measures ANOVA.

Discussion

Single-pulse TMS to the right FEF improved visual discrimination of still dots while participants performed a reflexive eye movement (the optokinetic nystagmus) in response to background motion of the visual scene (optokinetic stimulation). rFEF TMS also slowed the slow phase velocity of these eye movements on those same trials, when the target dot was still. Very different effects occurred when participants instead fixated on a central point, but otherwise continued to view background motion and to perform the task: worse visual perception occurred after rFEF TMS when the target dot moved leftwards, and was associated with an abolishment of frontal-posterior balance in alpha-band oscillations. Below we interpret these results to demonstrate multiple, dissociable roles of the rFEF during optokinetic stimulation and optokinetic nystagmus.

Right FEF TMS facilitates visual perception and impairs eye movements during OKN

Two different behavioral effects of right FEF TMS on target dot motion discrimination during optokinetic stimulation are reported here: an improvement in discrimination of still stimuli during OKN and an impairment at discrimination of leftward moving dots during fixation. FEF stimulation improves detection of still flashed stimuli in monkey (Moore and Fallah 2001; Thompson and Schall 1999; Armstrong and Moore 2007) and human (Grosbras and Paus 2002, 2003; Chanes et al. 2012; Quentin et al. 2013; Bosch et al. 2013). Behavioral and neural effects imply that it is as if the FEF stimulation modulates an attentional signal

(Moore and Fallah 2001; Armstrong and Moore 2007). Although the optokinetic nystagmus is primarily controlled by circuits in the brainstem and cerebellum (e.g. Ruehl et al. 2017; Gulyás et al., 2007; Hoffmann et al., 2004 the FEF is also important for generating some kinds of eye movements (Gottlieb et al. 1994; Grosbras et al. 2005) and FEF lesions impair eye movements and decrease OKN gain (Pierrot-Deseilligny et al. 1991; Rivaud et al. 1994). Optokinetic nystagmus is affected by visual attention (Williams et al. 2016; Rubinstein and Larry 2011), for example if participants are instructed to attend to one of two simultaneously presented optokinetic stimuli (Kanari et al. 2017). Importantly for the current results, attention also affects the suppression of nystagmus. Participants can suppress an optokinetic nystagmus in the presence of a clearly stationary object, such as the fixation point in the fixation blocks (Ter Braak 1936; Murasugi et al. 1986) or even an attended afterimage (Howard et al. 1989). Attending away from the fixation point during nystagmus suppression weakens the suppression (Williams et al. 2006). Given FEF TMS facilitating performance during attentional tasks, and attention modulating nystagmus suppression, we would speculate that the FEF TMS pulse in the current experiment may also have had effects similar to that of attentional orienting to the still dot targets. With additional attention, the signal from those dots would become perceptually stronger (Carrasco 2011) enabling them to act to suppress the nystagmus. This interpretation accounts for why rFEF TMS during OKN improved perception and yet slowed the slow phase of the OKN, when the dot was still. On the other trials, the target dot was moving and with an unpredictable velocity that varied from trial to trial, and so did not provide a stable reference on the basis of which the nystagmus response could be successfully suppressed.

Without TMS, slow phase velocity was not normally affected by dot direction: the dot onsets did not on their own distract the eye movement system from generating the saccade. Note that this eye movement velocity decrease occurred during that same task condition associated with improved visual perception (still dot trials). A previous study using TMS over the right FEF reported a similar pattern: TMS applied after an endogenous spatial cue slowed saccades to the indicated target, and the strength of this correlated across participants with the extent to which FEF TMS facilitated performance on separate blocks without eye movements but when the cue instead indicated a covert shift of attention to a visual target presented later (Taylor et al. 2006). Future work can examine whether these differences may be due to the timing of the pulse relative to the event measured (before or after the visual stimulus, before or after the eye movement command signal) or feasibly the spatial precision of the task (an eye movement is to one location, a response to a visual stimulus could be enhanced by facilitating processing over a wide region of space).

Previous FEF TMS studies of other types of eye movements

The bulk of the extant literature on FEF and visual stability has not looked at visual reafference (visual input arising as a result of the eye movement) but rather on the use of a different cue for visual stability, corollary discharge. This is because that work has largely investigated saccades, eye movements which are so fast that visual input during the eye movement is blurred beyond being useful, and is even suppressed (Bridgeman 2011). During oculomotor competition, where targets and distracters are presented simultaneously, FEF TMS encourages saccades to deviate away from the distractor (Walker et al. 2009) and reduces saccades to a distractor in visual search (Bosch et al. 2013). Theta burst FEF TMS distorted perception during transsaccadic stimulus displacements as if participants were effectively underestimating the amplitude of the performed saccade (Ostendorf et al. 2012).

The current study extends the role of the right FEF in visual perception into the domain of slow eye movements occurring in optokinetic stimulation.

rFEF in the context of a cortical network

Future work can test whether these results are selective to the brain area selected here, or whether similar effects could be found stimulating a different cortical region involved in vision, attention and eye movements, for example the parietal eye fields. One interesting (although speculative) possibility is that other areas within the dorsal attentional network may also play a causal role in motion discrimination. It is important to underline that the focus of this project was not on the investigation of the FEFs in general (i.e. left and right) during this task. Although it is theoretically possible that the left and right FEFs are symmetrically arranged such that each is responsible for a particular motion direction, it is also plausible that the left FEF may not have simply the mirror-image function of the right FEF. Here the right hemisphere was chosen, because in the field of higher vestibular cognition, it has been suggested that the right hemisphere (in right handers) may be specialized for vestibular cognitive processing (Dieterich and Brandt 2015). During OKN, the FEFs are activated independently from background motion direction (Konen et al. 2005), and right FEF is more activated than left (Dieterich et al. 1998). In addition, some previous studies have shown a greater effect on attention after right FEF-TMS than left FEF TMS (e.g. Grosbras and Paus, 2002, 2003, Muggleton et al. 2003). Accordingly here we focused on the function of the right FEF. Relatedly, an additional prospect for future work is to investigate effects with optokinetic stimulation moving in other directions (e.g. rightward, upward, downward) and whether right FEF TMS has a similar effect on leftward dots presented on a rightward moving background. Note however that this additional condition is not a necessary prerequisite for demonstrating that the FEF TMS effect is specific: here the effects on task performance, optokinetic nystagmus, ERP and EEG alpha power were specific to the direction of motion of the target dot. In this study, it was crucial to measure target dot perception relative to the visual reference frame (OKS) and so the background direction and speed was kept constant.

Perceptual function of the right FEF

FEF has diverse functions spanning from perception to eye movements and the interactions between them (Vernet et al. 2014). This is evident in the initial report of visual, motor and visuomotor neurons (Bruce and Goldberg 1985), different connectivity patterns (Ninomiya et al. 2012), massive connectivity (Markov et al. 2013) and the more recent clustering into 10 visuomotor categories reflecting the numerous functions of the FEF (Lowe and Schall 2018). In this study, FEF TMS had an additional effect: during the fixation blocks visual discrimination was impaired on leftward moving dot trials. This result cannot be explained solely by the difficulty of the task; performance was also reduced in leftward dot trials during OKN and there TMS did not have an impact on the behavioral response. It should be noted that the impact of FEF TMS on visual performance is far from always facilitatory. rFEF TMS increases the cost of attentionally demanding trial types (Grosbras and Paus 2002; Duecker et al. 2013; Hung et al. 2011 Muggleton et al. 2003; Esterman et al. 2015; Chen et al. 2018) particularly contralateral to stimulation (Marshall et al. 2015b). FEF TMS affects how attention modulates drift rates during perceptual decision making (Rahnev et al. 2016). FEF recording in macaques discriminating motion direction in random dots also supports a role in perceptual decision making (Ferrera et al. 2009; Ding and Gold 2012; Purcell et al. 2012). According to this perspective, here right FEF TMS impaired making the perceptual decision that the dot moved to the left. This accounts for why rFEF TMS had no effect on “leftward” motion during the OKS blocks: the OKS grating always moved to the left and the dot, even on leftward trials, moved more slowly than the grating. Therefore during the slow leftward eye movements, the dot would not have provided any leftward motion signal on the retina: rather here rFEF TMS only affected processing leftward motion (relative to gaze, which occurred on fixation blocks). The plurality of FEF neuronal subtypes, however, allows multiple functions within this area including trans-saccadic stability (Joiner et al. 2013; Chen et al. 2018; Crapse and Sommer 2012). Other aspects of visual motion processing involving other reference frames may be represented elsewhere in the brain: posterior parietal cortex (PPC) TMS and not FEF TMS affected trans-saccadic fusion and predictive position estimates (Edwards et al. 2017; Chen et al. 2018) and TPJ TMS can impair OKN suppression (Haarmeier and Kammer 2010).

Effects of right FEF TMS on neural activity

Attention (Kelly et al. 2006; Thut et al. 2006) and demanding tasks (Händel et al. 2007) can modulate alpha oscillations. High pre and post-stimulus alpha power predict impaired visual detection performance, and vice versa (van Dijk et al. 2008; Babiloni et al. 2005; van Diepen et al. 2016). Attention directs alpha in order to block the process of irrelevant information (Händel et al. 2011). FEF TMS affects posterior visual activity (Silvanto et al. 2006; Taylor et al. 2006; Capotosto et al. 2009; Ruff et al. 2006; Cocchi et al. 2016); right FEF TMS may act through disrupting the normal interaction between right FEF and posterior visual cortex (Sauseng et al. 2011). Accordingly, here the normal difference in alpha power between frontal and posterior brain regions was abolished in leftward trials during the fixation block (Fig.9). Decreased accuracy after right FEF TMS may then originate in the relative levels of alpha activity across frontal and posterior sites. A part of normal FEF function may be to not only control posterior inhibitory alpha (Sauseng et al. 2005) but maintain the balance between frontal and posterior regions (Sauseng et al. 2011). In addition, right FEF TMS boosted the late part of the right frontal ERP, which was also normally modulated by dot direction without TMS.

A task specific effect of TMS was observed, for leftward moving dots and still dots. Note that visual-evoked potentials (VEPs) and TMS-evoked potentials (TEPs) do not replace one another but add together (Thut et al. 2003), and so the lack of any TMS effect on rightward moving dots cannot be explained by the larger amplitude of the ERP on rightward trials observed at baseline. Given that the rightward VEP is already large in amplitude without TMS, if a TEP is added on top of that, we would expect even larger components if the TMS effect was not task specific (see Fig.6, panel A). Late pre-frontal positivities reflect perceptual decision making (Potts 2004; Gajewski et al. 2008; Gajewski and Falkenstein 2013; Berchicci et al. 2016) and stimulus evaluation (VanRullen and Thorpe 2001). Note that the TMS effects on ERP amplitudes and alpha modulations were different. rFEF TMS affected the late frontal ERP for both leftward motion and still dot trials, whereas time-frequency analysis showed TMS influenced frontal and posterior alpha power only for leftward motion trials. There are dynamics in the EEG data that are not visible in the ERP and for which a time-frequency based approach is more sensitive (Cohen, 2014). Occipital alpha rhythms may reflect cyclic perceptual processes (Samaha and Postle 2015; VanRullen 2016), and generally many aspects of cognition results from the coordination of temporally discrete cognitive computations orchestrated by neural oscillations (e.g. Buschman and Miller 2010).

Conclusion

These results show that the rFEF plays a causal role in perception and oculomotor control during optokinetic stimulation. This extends previous work reporting correlations between rFEF activity and OKN (e.g. Dieterich et al. 1998), or that found a causal role for rFEF in the interactions between perceptual and oculomotor control during saccades (e.g. Walker et al. 2009, Bosch et al. 2013, Ostendorf et al. 2012). The FEF is well-placed to orchestrate visuomotor interactions. Previous work has generally explored this with other types of eye movements, like saccades. The current work extends this in to the domain of the slow visual motion and eye movements occurring during optokinetic stimulation. This type of stimulation may in the future act as a model for the slow visual motion stimulation and oculomotor responses that occur as we interact and move through the environment. There may be multiple computational and neural overlaps between the systems for vision and navigation (Nau et al. 2018).

Declarations of interest: none.

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2.2 Study 2: Right frontal eye field TMS increases visual perception and modulates posterior alpha oscillation during optokinetic nystagmus

Right frontal eye field TMS increases visual perception and modulates posterior alpha oscillation during optokinetic nystagmus

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Abstract

In this study, we investigated whether the behavioral effect of the right frontal eye field (rFEF) TMS observed during optokinetic nystagmus (OKN) and described in our previous work (see Chapter 2.1), could be reflected in a specific brain response. The facilitatory effect of rFEF TMS was specific for the condition where participants had to discriminate still stimuli (dots) despite the generation of reflexive eye movements. This visual perceptual finding was accompanied by a change of the oculomotor response specific for this condition: decreased slow phase velocity of nystagmus followed rFEF TMS during the discrimination of still dots. These effects were not found in other dot direction conditions during OKN (leftwards dots and rightwards dots), nor during the same visual motion discrimination task performed keeping the eyes stationary (fixation block). The effect was specific for rFEF, and no effects were found after control site stimulation. We expected a neural correlate of the facilitatory TMS effect seen at the behavioral level to be found for still stimuli, could be found in the time domain or in the time-frequency domain of the EEG data, and we focused on rFEF influences on the modulation of ERP components and alpha oscillations. Specific

rFEF TMS modulation during the presentation of still dots was found in the level of alpha power recorded from posterior sites. Taken together, our results suggest that the rFEF is a crucial region for modulating visual perceptual processes even during ongoing reflexive eye movements, and this seems to be associated with reduced eye movement velocities and with a specific alpha modulation over posterior cortex.

Introduction

The frontal eye field (FEF) is a brain region that has been largely described for its oculomotor control and for its visual perceptual functions. Despite the strong relationship between action and perception these two functions have often been studied separately. Human (Grosbras and Paus 2002, 2003; Bosch et al. 2013a; Quentin et al. 2013a) and animal (Thompson and Schall 1999a; Moore and Armstrong 2003; Moore and Fallah 2004) studies demonstrated a crucial role played by FEF in visual stability and visual awareness. Although previous studies investigated whether the FEF was relevant for eye movements and also for the consequences of eye movements (Moore and Armstrong 2003; Moore and Fallah 2004), these works focused on one type of eye movement, on saccades, in relation to visual stability. For other types of eye movements, for example slow eye movements such as pursuit, the demands on visual stability may be different than what occurs during saccades: the suppression of the visual input during saccades cannot help with visual stability (Bridgeman 2011). Smooth pursuit eye movements are often performed in the presence of a moving background, and the ocular response changes when the moving visual scene is perturbed (Spering and Gegenfurtner 2007; Spering and Montagnini 2011; Haarmeier and Kammer 2010). Although the role of the FEF has been largely studied in relation to saccades the function of this brain area in solving the perceptual consequences of slow eye movements remains unclear.

Evidence from other studies show that stimulation of the FEF affected perception; FEF TMS delivered before target onset decreased the visual perceptual threshold in a detection task when applied over the right hemisphere (Grosbras and Paus 2002; Chanes et al. 2012). Taken together these findings, we devised a novel task in order to measure eye movements and visual perception simultaneously while right FEF (rFEF) was stimulated by single pulse TMS. Our aim was to understand the cognitive mechanism behind the ability to perceive stable objects that we are surrounded by, regardless of the eye movements that are in everyday life generated in response to optic flow. In order to do that reflexive eye movements (optokinetic nystagmus, OKN) were elicited by a moving visual scene (optokinetic stimulation, OKS, Ilg 1997; Kowler 2011). This type of eye movement with a slow phase (smooth pursuit) in the direction of the moving background and a quick phase in the opposite direction (resetting saccades) to some extent models what occurs while we navigate our environment. In the previous study we observed that during fixation (see Chapter 2.1), that is when participants were fixating on a moving background and no eye movements were elicited, rFEF TMS impaired visual performance measured at the behavioral level, and it was associated with the abolition of the normal balance between frontal and posterior alpha oscillations (Mastropasqua et al. 2019).

Here we hypothesized that the improvement in visual perceptual discrimination observed (despite the ongoing OKN) at the behavioral level, as described in our recent work, could also be apparent at the neural level. We expected specific neural correlates associated with the perceptual enhancement of still stimuli induced by TMS compared with baseline. In particular, we predicted a specific alpha modulation induced by TMS during the discrimination of stationary stimuli despite eye movements in the group that received the stimulation over the rFEF. Previous studies suggested that the FEF is crucial for visual perceptual modulation and visuo-spatial attention showing evidences of the FEF influence over posterior alpha oscillations (Capotosto et al. 2009; Sauseng et al. 2011; Marshall et al. 2015).

Methods

For full details of the methods see paragraph “MATERIALS AND METHODS”, Chapter 2.1. Briefly, a combined TMS-EEG study was performed in order to investigate the causal role of the right FEF in resolving the visual perceptual consequences of reflexive eye movements. In addition, a head-mounted eye tracker system was used to record any change in the slow phase velocity of nystagmus following FEF stimulation. Any dissociation of the visual perceptual and oculomotor control functions of the FEF was tested with a task where optokinetic stimulation was combined with a visual motion discrimination task. More specifically, bright dots and grey and black bars, moving coherently in one direction (leftwards), were simultaneously presented (see fig. 1, Chapter 2.1). Participants were required to discriminate the direction (left, still or right) of dots that were briefly (100 ms) presented in the upper or lower part of the screen. Dots were displayed with a random order and the ISI ranged between 4000 and 5000 ms. Three types of dots were shown with equal probability: leftwards dot, still dot and rightwards dot. The task was to discriminate as quickly and as accurately as possible the direction of dots (by buttons press, using the right hand) while looking passively in the middle of the screen (OKN block) or while they were keeping their eyes stationary (fixation block). Given that the aim of the study was to investigate the perceptual consequences of reflexive eye movements, the background speed was kept constant (33°/s) whereas the dots were moving at random speeds, ranging from 1 to 32 °/s, to ensure visual stimuli (dots) unpredictability. In order to explore the causal role of the FEF during this task, thirty-two participants took part in the experiments, half of them received TMS over the rFEF and the remaining half had the stimulation over the control site, right primary motor cortex (rM1, see fig. 2, Chapter 2.1).

In the previous project we analyzed the modulation of the FEF-TMS during the fixation block, when participants were fixating on a fixation cross over impose on a moving visual background. In this chapter by contrast the data during the eye movement blocks is analyzed. The methods developed in order to clean the data from artefacts due to eye movements were validated in the third project (see paragraph *"EEG acquisition and pre-processing"*, Chapter 2.3) and allowed us to investigate not only the neural correlate of motion discrimination during OKN but also the causal role played by the right FEF in dealing with the perceptual consequences of reflexive eye movements, such as OKN.

As described in Chapter 2.3, EEG data were filtered (notch 50 Hz filter and a Butterworth zero phase filter, bandpass 0.1 Hz to 40 Hz, Luck 2014) and the TMS pulse artefact was removed by linear interpolation (5 ms before and 45 ms after TMS pulse onset). Later the data were segmented to 1000 ms pre and 2000 ms post dot onset. Data were baseline corrected to the 1000 ms before dot onset. Fast-ICA (Hyvärinen and Oja 2000) was performed on all segments to identify and remove the "OKN component" from the EEG signal (see Fig. 2, Chapter 2.3). After the EEG signal was cleaned from the OKN related artefacts, the data were further pre-processed to run the ERP and the time-frequency analyses. The same procedure executed on EEG data during fixation (see for details paragraphs *"Event-Related Potential Recording" and "Time-Frequency Analysis",* Chapter 2.1) was performed on the signal recorded during OKN. In brief, ERPs were built from epochs starting 100 ms before and ending 399 ms after dot onset. Following the evoked potentials elicited by stimuli with TMS and stimuli without TMS (baseline) were subtracted, per each dot type direction: leftwards dot, still dot and rightwards dot. Unlike the analyses described in Chapter 2.1, where ERP amplitudes were compared between TMS and no-TMS trials, here we tested TMS-evoked potential (TEP) differences between the two blocks (OKN and fixation). The same approach was used for the time-frequency analysis, alpha power modulations were tested on the difference between the level of alpha induced by TMS and the level of alpha at the baseline. Short-time Fourier transform (STFT) was performed on segmented data starting 300 ms before and ending 300 ms after dot onset. The power was extracted from the alpha-frequency range, from 8 to 12 Hz.

This design for the analysis, looking at the difference between TMS and baseline, offered a better way to investigate potential TMS context-specific modulations. The visual facilitation induced by rFEF TMS during the discrimination of still stimuli was specific to the OKN block, no visual perceptual improvement occurred following rFEF TMS during fixation nor after the stimulation of the control site.

In the following analysis, the TMS-evoked potential (TEP) and the alpha power induced by TMS (TMS minus baseline) were entered in a repeated measures ANOVA with two within-subjects factors, dot direction (left vs still vs right) and block (fixation vs OKN) and one between-subjects factor, group (rFEF vs rM1). In the TEP and time-frequency analysis, time bins and channels were selected on the waveform showing the difference between still and leftward dot motion trials at baseline during OKN. These were the two conditions presenting the biggest difference at the behavioral level. In the time-frequency analysis, fifteen out of sixteen participants per group were included in the analysis; one participant from rFEF and one from rM1 group were excluded due to there being fewer than 30 trials per conditions after data pre-processing (following this, the analyses on behavioral and ERP data were also performed without these two subjects and the results remained unchanged).

Results

TMS evoked potentials

The aim of the following analysis was to investigate whether a neural correlate of the TMS effect observed for still trials at the behavioral level during OKN (see Fig. 1), was also present in the ERPs. The task specific TMS effect found on the behavioral data was that FEF-TMS increased the frequency of correct responses at correctly discriminating that still dots were indeed still, during continuous OKN.

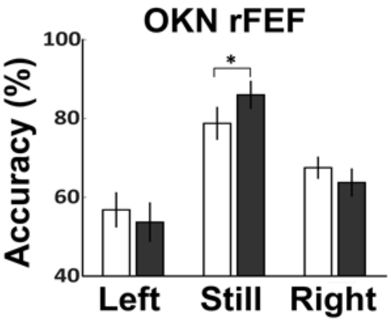


Fig. 1: *rFEF TMS increased significantly accuracy (correct responses) during the discrimination of still dots, in OKN blocks. Behavioral performance at baseline, averaged across participants, is represented with blank bars; black bars indicate accuracy following stimulation of rFEF. Error bars show standard error from the mean (SEM).*

TEPs were derived (TMS minus baseline) for each dot direction (left, still, right) and block (fixation and OKN). Two time bins and two groups of electrodes were selected from the ERP amplitude difference comparing still and leftward trials, in OKN blocks (see Fig. 2). Early differences (30- to 60 ms) were found at the posterior channels Pz, PO4 and O2. Later (160- to 190 ms) and clear differences were observed at frontal sites, Fz, FCz and F1. A posterior region of interest (ROI) and a frontal ROI were defined, ERP amplitudes were extracted from the time bins selected and averaged between the channels forming the ROIs.

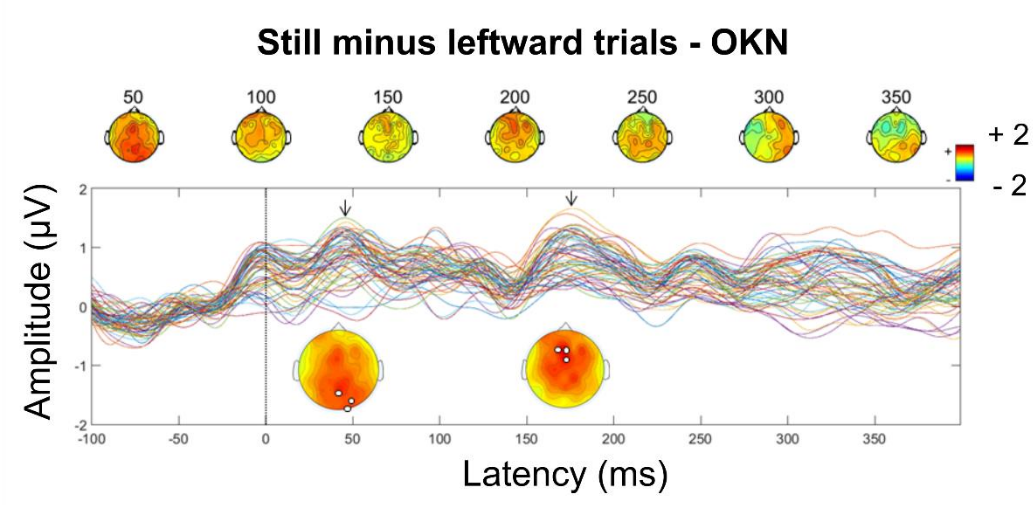
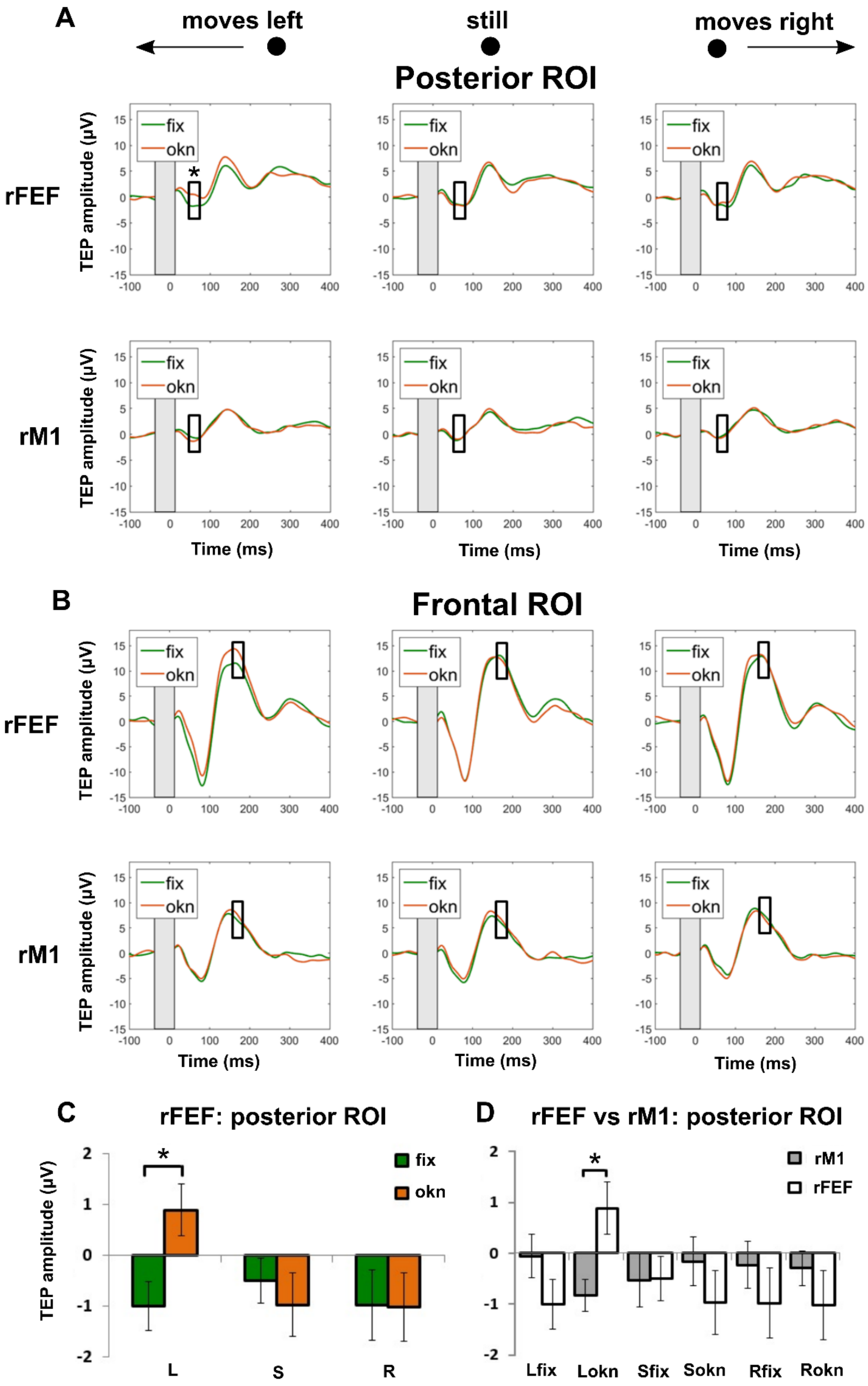


Fig. 2 *Butterfly plot and topographies of the still-minus-left TEP amplitude difference during OKN. All the recording channels from the scalp are overlaid. The biggest differences are indicated with arrows around 45 ms and 175 ms after dot onset (which was time zero). Two time bins were defined spanning 15 ms before and after the peak observed, resulting in 30- to 60 ms and 160- to 190 ms time bins. The scalp distribution of TEPs was averaged within the two time bins as presented in the two topographies below and the channels presenting the biggest difference are illustrated with white circles.*

There was no specific TMS modulation in the time bins and channels selected that could explain the improved performance observed for still trials in the OKN block and not during fixation. The analysis performed on the amplitude values extracted from the posterior ROI showed a three-way interaction between dot direction, block and group ($F(2,60) = 6.26$, $P < 0.01$). Two-way interactions between dot direction and group, block and group and, dot direction and block did not reach statistical significance (all P's > 0.05). Subsequent independent t-tests were run between rFEF and rM1 TEPs per each dot direction (left, still, right) and block (fixation and OKN), with the only significant difference found on leftward OKN trials ($t(30) = 2.95$, $P < 0.01$, see Fig. 3, panel D). rFEF TMS increased whereas rM1-TMS decreased ERP amplitudes compared to baseline. No significant effect was found in the analysis performed on the frontal ROI: TMS induced ERPs did not differ between fixation and OKN in any dot direction and no interactions were found including the factor group (all P's > 0.05, see Fig. 3, panel B).

Further analysis was performed to investigate the TMS modulation over the rFEF and the rM1 separately: no main effects or interactions were found in the rM1 data (all P's > 0.05), in either posterior or frontal ROIs. An overlap between the two waveforms (Fixation and OKN) can be observed for the time bins and for both posterior and frontal ROIs, for the control site (rM1, see black rectangles in Fig. 3 second row, panel A and B). The same analysis on the posterior ROI showed different results in the rFEF group: TMS differently affected neural activity evoked by leftward visual stimuli during fixation compared to OKN (see Fig. 3, panel C). A main effect of dot direction ($F(2,30) = 3.87$, $P < 0.05$), a marginal main effect of block ($F(1,15) = 4.50$, $P = 0.05$) and a significant interaction between the two factors ($F(2,30) = 5.89$, $P < 0.01$) were found. A subsequent paired t-test between fixation and OKN in each dot direction presented significant differences for leftward trials ($t(15) = -$

4,69, $P > 0.001$) but not for still and rightward trials ($t(15) = 0.82$, $P = 0.43$ and $t(15) = 0.10$, $P > 0.9$, respectively). There were no effects in the frontal ROI for the rFEF group (all P's > 0.05).


A
moves left
still
moves right
Posterior ROI
rFEF
rM1
TEP amplitude (μV)
fix
okn
*
Time (ms)
B
Frontal ROI
rFEF
rM1
TEP amplitude (μV)
fix
okn
Time (ms)
C
rFEF: posterior ROI
TEP amplitude (μV)
*
fix
okn
L
S
R
D
rFEF vs rM1: posterior ROI
*
rM1
rFEF
Lfix
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Sfix
Sokn
Rfix
Rokn

Fig. 3 *TEPs elicited by leftward, still and rightward dots (as represented by dots and arrows on top of each plot) from the posterior ROI (panel A) and frontal ROI (panel B). Waveforms from fixation block are in green and the waveforms from OKN are in orange. Data from both group are shown, rFEF (first row, panel A and B) and rM1 (second row, panel A and B). Time bins selected from posterior and frontal ROI are indicated with black rectangles. In panel C, mean TEP amplitudes extracted from the posterior ROI in rFEF group are shown per each dot direction comparing the two blocks (fixation vs OKN). The same TEP values are compared between groups in each dot direction and in each block (panel D). Brackets and asterisks indicate significant differences.*

Alpha power

A further analysis on alpha power investigated if a selective rFEF-TMS modulation occurred in still trials during OKN compared to fixation. In this analysis we tested whether the behavioral rFEF-TMS effect on visual discrimination during OKN (that did not have a correlate in the TEP analysis) could be found in the alpha power, which is highly related to visual perception. Attention and demanding tasks can be reflected in the alpha frequency (Klimesch et al. 1998; Thut et al. 2006). In order to do that, short-time fast Fourier transform (FFT) was performed on all channels for the three different types of trial (left, still, right) during OKN, as done previously during fixation. Target-induced alpha power was compared between experimental conditions in the 300 ms window after stimulus onset in the alpha range (from 8 to 12 Hz) (for details see Chapter 2.1, paragraph *Time-Frequency Analysis*). The alpha power distribution was explored on the difference between still and leftward trials at the baseline during OKN, as done above for the TEP data. This difference was examined in order to identify channels and times reflecting the improved visual performance during still versus leftward trials. Electrodes and time bins showing the biggest differences were selected; two peaks in the alpha power difference were found at 100-120 ms and 140-160 ms time bins after dot onset. In the first time bin, the difference maximal at central posterior channels, Cp1, P3, PO3 and POz, and starting from 20 ms later the difference moved to a more right posterior location, PO8, P8, TP8 and PO4 (see Fig. 4).

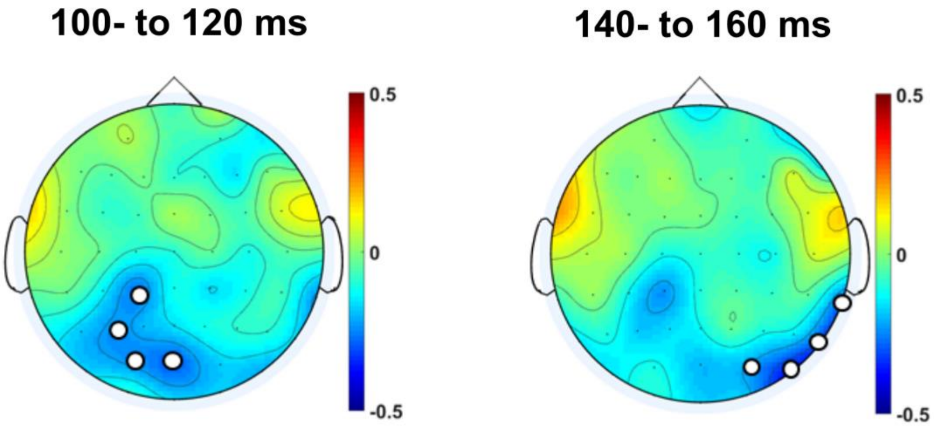

Fig.4: *Topographies of alpha power distribution across the scalp, showing the difference between still and leftward moving dot trials. Panel on the left: alpha power distribution across 100- to120 ms time bin after dot onset. Panel on the right: values averaged across 140- to160 ms time bin following dot onset.*

The selected electrodes formed two ROIs, one central-posterior and one right-posterior. As done to test rFEF TMS induced alpha modulation during fixation block (see Chapter 2.1), here the TMS induced alpha power (difference between TMS and baseline)was calculated and compared between blocks (fixation vs OKN) in each dot direction, for rFEF and in rM1 groups. The same mixed factorial ANOVA design used on TEP data was performed on the TMS-induced alpha power values in order to test for a selective modulation of alpha following rFEF TMS during the discrimination of still stimuli. The central-posterior

ROI presented a main effect of block ($F(1,28) = 4.7$, $P < 0.05$) and a two way interaction between dot direction and block ($F(2,56) = 4.83$, $P < 0.05$), but no significant interactions were found with the group factor (all P’s > 0.6). The same findings were found when alpha power differences were tested in the right-posterior ROI, with no interactions between dot direction, block and group ($F(2,56) = 1.06$, $P > 0.05$) but a main effect of block and an interaction between dot direction and block were significant ($F(1,28) = 4.91$, $P < 0.05$ and $F(2,56) = 3.98$, $P < 0.05$, respectively). Considering the significant interaction found between dot direction and block, in both ROIs and taking into account the lack of main effect of dot directions ($F(2,56) = 1.3$, $P > 0.05$ for central-posterior ROI and $F(2,56) = 1.14$, $P > 0.05$ for right-posterior ROI), subsequent paired-test were performed in each group, and the TMS induced alpha during fixation and OKN was compared for each dot direction. Significant alpha power differences were found in rightward moving dot trials, in the central posterior ROI, in both the rFEF ($t(14) = -2.41$, $P < 0.05$) and in the rM1 group ($t(14) = -2.18$, $P < 0.05$). In the posterior-right ROI, the t-tests between fixation and OKN showed significant differences in the rightward trials, for both groups ($t(14) = -2.79$, $P = 0.02$, rFEF and $t(14) = -2.40$, $P < 0.05$, rM1) but interestingly differences in still trials were observed only in the rFEF group ($t(14) = -2.32$, $P < 0.04$) (see Fig. 5).

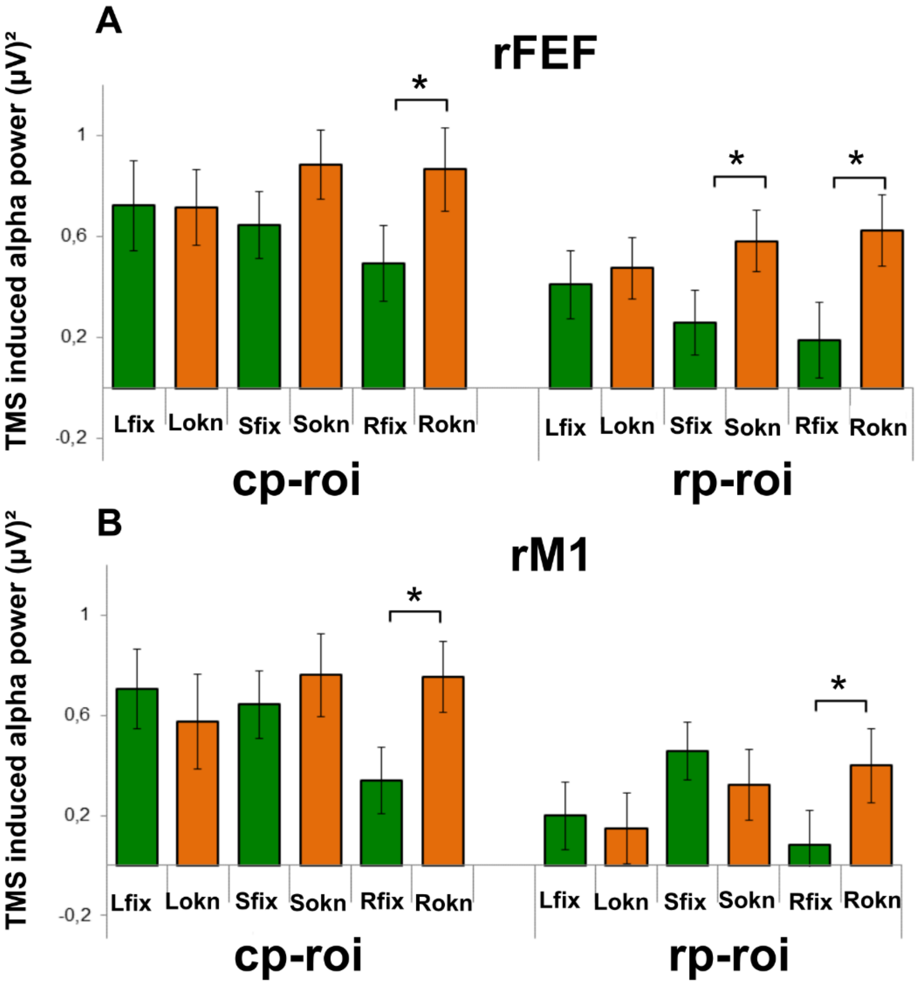

Fig. *5 Alpha power during fixation (green bars) and during OKN (orange bars) per each dot direction from the central-posterior ("cp-ROI", on the left of each plot) and right-posterior ("rp-ROI", on the right) ROIs, for rFEF (panel A) and rM1 (panel B). Each bar represents the subtraction between alpha power induced by TMS and alpha power at the baseline. Significant differences between blocks in each dot conditions are indicated with asterisks.*

Discussion

The changes induced by rFEF TMS in the TEPs and in the alpha oscillation contribute to our understanding of visual perceptual processes during reflexive eye movements. The TEP findings did not reveal any specific rFEF TMS effect for still trials on fixation compared to OKN blocks, as expected. In fact, despite that the visual perceptual facilitation registered during the discrimination of still stimuli after rFEF TMS was specific for the OKN blocks, there were no differences in the TEPs between the two blocks. Instead, a significant difference at the early time bin and in the posterior ROI was observed in leftward trials. This early response was evoked by stimuli that were moving in the same direction as the optokinetic stimulation when preceded by TMS. The TMS effect on the early component (~ 50 ms after dot onset) found only in leftward moving trials was significantly different between the two blocks, fixation and OKN, with more negative amplitudes registered during fixation (see Fig. 3, panel A). One possible explanation is that the amplitude at this time could have been modulated by the level of difficulty of the discrimination task, and the discrimination of leftward moving stimuli while the background moved coherently to the left represented the most difficult condition for visual motion discrimination. In a fMRI study combined with EEG, early modulation in extrastriate visual area was described as the consequences of a delayed feedback from higher visual areas or of a sustained bias during attention (Martínez et al. 1999). A differential early response in parieto-occipital ERPs was observed between tasks measuring contextual landmarks and perceptual discrimination (Lambert and Wootton 2017).

Different effects were found in the time-frequency domain on alpha oscillations. FEF is crucial for visual perception (Grosbras and Paus 2002; Ruff et al. 2006; Marshall et al. 2015) and visual performance is associated with alpha power (Hanslmayr et al. 2005). Moreover, parietal and frontal stimulation, including FEF TMS, modulate alpha power in parieto-occipital sites (Thut and Miniussi 2009 for review) and the pre-frontal cortex has been suggested to control visual attention via posterior alpha (Sauseng et al. 2011). In our data, a significant difference in the TMS induced alpha power between fixation and OKN was found in rightward trials and this effect was observed in both groups, following stimulation of rFEF and also of rM1. In detail, higher levels of alpha were TMS induced while participants were discriminating dots moving to the right (during the generation of leftward OKN), and this effect was not specific to the TMS site and was not associated with any modulation at the behavioral level. The same TMS modulation found in both experimental groups cannot be due to a non-specific TMS artefact, as the effect was task specific and it occurred only when contralaterally moving stimuli (relative to background direction) were discriminated. One interpretation for these findings is that this effect might be due to higher alpha modulation being necessary for ignoring the visual input relative to the moving visual scene. Indeed alpha activity might reflect a mechanism of active attentional suppression; an increase in alpha power has been consistently found in the visual cortex contralateral to an ignored visual hemifield (Worden et al. 2000; Kelly et al. 2006).

The increase in alpha power following TMS was bigger during OKN than fixation, for rightward trials in central and right posterior sites. In the light of previous work, increases or decreases in alpha oscillation depend on task demand: for example much work supports a contribution of alpha modulation in the biasing of visual attention (Foxe et al. 1998; Worden et al. 2000; Fu et al. 2001). Here we can speculate that this alpha modulation recorded during the discrimination of rightward stimuli, evident as a bigger alpha power increase during viewing contralateral moving visual scene compared to fixation, might be driven by the perception of stimuli moving to the right during leftward optokinetic stimulation initiating a suppression of the moving background in order to maintain a vivid image of the dot moving to the right. The early alpha modulation (at ~110 and at ~150 ms after dot onset) that occurred with contralaterally moving stimuli in both groups may indicate the provision of an accessible visual reference used to ignore the moving visual scene, and paying attention to contralaterally moving stimuli. A further consideration it might be that these alpha differences indicate systematic change in motion perception that will not be revealed the way the experiment was performed.

Specific to rFEF TMS was the alpha modulation in right posterior recording sites during still trials. The alpha power induced by rFEF TMS was higher during the discrimination of stationary stimuli in OKN than in fixation, and this was associated with an improvement of visual perceptual performance. FEF TMS affects visual perception through the modulation of posterior brain activity (Ruff et al. 2006; Silvanto et al. 2006; Taylor et al. 2006; Capotosto et al. 2009) and attention modulates alpha in order to ignore irrelevant information (Kelly et al. 2006; Händel et al. 2011). As described in our previous work (Mastropasqua et al. 2019, see Chapter 2.1) during the discrimination of still stimuli, rFEF improved visual performance despite continuous reflexive eye movements, and this occurred with a reduction of the slow phase velocity of nystagmus. Previous studies have drawn a relationship between level of alpha during OKN and visual attention; alpha rhythms in the occipital cortex corresponded to a reduction in the slow phase velocity, and alerting stimuli such as vibration and sound increased the nystagmus velocity (Magnusson et al. 1985). Cortical mechanisms during the generation of passive OKN, also called “stare-OKN”, are additional detectable as decreased parieto-occipital alpha power (Gulyás et al. 2007) and as an increased BOLD signal in the temporo-occipital cortex, in supplementary, frontal and parietal eye field and prefrontal cortex (Dieterich et al. 2003). Other studies have shown a greater signal from the occipito-temporal cortex during smooth pursuit of a moving dot, compared to viewing a moving grating but keeping the eyes still (e.g. Barton et al. 1996; Dieterich et al. 1998), and here we found a significant difference between TMS induced alpha power during OKN and in fixation.

Perturbation of frontal oculomotor regions with TMS during smooth pursuit affects eye velocities and the direction of this effect depends on when the stimulation is delivered relative to the cycle of the target in motion (Gagnon et al. 2006). Electrical recording in monkey FEF during both smooth pursuit and visually guided tasks has demonstrated the presence of the neurons that responded only during smooth pursuit tracking of moving stimuli and had no responses during visual guided saccades. These neurons were classified as "pursuit neurons" (Gottlieb et al. 1994). Patient studies showed that after FEF ischemic lesions the OKN slow phase velocity decreased (Rivaud et al. 1994). Both the motor and attentional roles of FEF have been demonstrated in several studies (e.g. Grosbras and Paus 2002, 2003), but the relationship between them has not been investigated during slow eye movements. Building on earlier findings we here show that the causal role played by the rFEF on visual perception and oculomotor response (described in details in Chapter 2.1) can also be demonstrated at a neural level. The specific alpha modulation registered during still trials despite eye movements is a further evidence of a process guided by the rFEF in order to resolve the visual perceptual consequences of reflexive eye movements. Both oculomotor control and visual perceptual functions of the FEF are crucial for the correct discrimination of stationary stimuli in the presence of reflexive eye movements. The visual perceptual manipulation induced by FEF stimulation was reflected in the facilitation of visual motion discrimination and in the modulation of alpha power: this latter seemed to provide the required level of alpha to ignore the moving visual scene to the benefit of improved visual discrimination of the stimuli.

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2.3 Study 3: Exogenous attentional orienting during optokinetic stimulation

Manuscript for submission

Exogenous attentional orienting during optokinetic stimulation

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Abstract

Although covert peripheral attention is a mechanism that we rely heavily on when we move in our environment, it remains unclear how this mechanism solves the perceptual consequences of reflexive eye movements and suppression of those eye movements. Our eyes respond continuously to optic flows generated by our motion in the world or by visual scenes in motion. We investigated this latter condition combining a visual motion discrimination task with optokinetic stimulation (OKS). Exogenous attention was modulated by peripheral stimuli, cues (hollow circles) presented at the same (valid) or at the opposite (invalid) location of impending targets (filled dots), while participants were looking passively at the middle of a moving background, in order to elicit a reflexive response, or while they were fixating on the moving background. Exogenous attention modulated the behavioral response and the brain activity in a similar way during ongoing reflexive eye movements and during fixation, a facilitation in the reaction times in valid compared to invalid trials was associated with a reduced P1 component. Attention modulated the perceptual judgment of stimuli presented with OKS and the perceptual processing of those stimuli but it did not affect the ocular response generated by the moving visual scene.

Keywords: exogenous attention, optokinetic nystagmus, slow eye movements, visual perception, ERP.

Introduction

Perceptual cognition and its neural correlates are often studied under carefully controlled lab conditions where participants keep their eyes still, for example to investigate covert peripheral perception, or to prevent results from being corrupted by overt eye movements. Despite many psychophysical studies directly addressing the interaction between eye movements and cognition, it remains unclear whether some key aspects of perceptual cognition operate in the same way during eye movements as during fixation, and whether the neural correlates are similar. The current study focuses on “exogenously” oriented visual spatial attention (Posner 1980b), referring to a “bottom-up” shift of attention that is automatic and externally driven. To implement the allocation of attention, exogenous cues (typically in the periphery) are presented as bright and brief stimuli, either at the location where the target will appear (valid) or somewhere else (invalid) (Yantis and Jonides 1984; Mulckhuyse and Theeuwes 2010). Visual attention (during fixation) affects perceptual performance and neural activity in visual cortex (Carrasco 2011, Jonides 1981; Posner 1980; Klein et al. 1992). Event related potentials (ERP) over posterior scalp sites suggest that the earliest reliable modulation by spatial attention occurs at the time of the early P1 component (latency 90-130 ms, (Mangun, G.R., 1995; Hillyard, S.A. and Anllo-Vento, L., 1998; Martín-Arévalo et al.

2016 for reviews), and this component is particularly dominated by exogenous attention (e.g. Hopfinger and West, 2006).

Despite the substantial literature on the effects of attention, it remains unknown whether these effects on behavior and the ERP are limited to fixation or also occur during eye movements. Eye movements are an ongoing part of daily life: for example, to perceive a clear visual scene during navigation, visually driven reflexive eye movements eliminate the retinal slip that would distort the visual input (Angelaki and Hess 2005b). The optokinetic nystagmus (OKN) is an eye movement generated in response to a moving visual stimulus (optokinetic stimulation, OKS, Ilg 1997, Kowler 2011) and plays a role in maintaining visual stability, for example if we navigate through the environment and the visual scene moves past us. The OKN is defined by a slow phase eye movement in the direction of the moving visual scene and a quick phase in the opposite direction. Some work has investigated the interaction between endogenous attention and OKN (Williams et al. 2006a; Kanari et al. 2017a) but it remains unclear whether exogenous attention can operate during the OKN.

Here, targets were presented in combination with optokinetic stimulation (OKS) and in two thirds of trials, brief valid or invalid cues preceded the targets. Our hypothesis was that it would be possible to demonstrate the modulation of behavior and the P1 ERP component by exogenous attention, during and despite ongoing continuous reflexive eye movements. An alternative possibility would have been that is strikingly harder or even impossible to orient exogenous attention during an OKN. This could be due to the competing demands put in place by performing these ongoing eye movements, processing the potentially distracting additional visual afferent input arising from the eye movement, and from other ongoing processes such as maintaining visual stability.

Measuring neural activity with EEG during eye movements raises challenges, due to signal artefacts, which can be addressed by Independent Component Analysis techniques (Makeig et al. 1996; Delorme and Makeig 2004; Delorme et al. 2007; Makeig and Onton 2012). Here a subsidiary aim was the methodological development of extending the application of ICA to OKN.

Materials and Methods

Participants screening

Thirty healthy volunteers (mean age 28 ± 6 years, 19 female) were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971) and gave informed consent for a protocol approved by the LMU Munich Medical faculty ethics committee. Participants had no prior history of neurological or psychiatric disorders, had normal or corrected-to-normal vision, and were compensated either with 9 euros per hour or course credit.

One participant was excluded due to performing below chance and three due to low quality EEG data (fewer than 30 trials per condition), leaving twenty-six (mean age 29 ± 6 years, 15 female). One additional participant was not included only in the eye movement analysis due to a technical fault with eyetracking (n = 25; mean age 28 ± 6 years, 14 female).

Exogenous attention during OKN

Stimuli were presented at 40 cm on an LCD monitor (1680 x 1050 pixel resolution, refresh rate 60 Hz). OKS background was 48° wide and 15° tall and composed of 19 black (RGB: 0, 0, 0) and 19 grey (RGB: 105, 105, 105) bars moving leftward at a constant speed of 33°/s (bar width 2.3 cm/3.3° VA). Targets, white dots (1.6 cm-diameter, RGB: 255, 255, 255), were presented for 100 ms at 15° eccentricity in the upper or lower hemifield. Dots moved from the midline either leftward, rightward, or were still, with equal probability. Dot location (upper vs lower), direction and speed (between 1 and 32 °/s) were all randomized. On two-thirds of trials exogenous attentional cues were presented 200 ms before target onset for 33 ms on the vertical midline either in the upper or lower field. The interval between cue and target was 160 ms (near to the peak facilitation for peripheral cued location, see Müller and Rabbitt, 1989). The task consisted of discriminating as quickly and accurately as possible whether the dots were leftward moving, still or rightward moving, responding with the right index, third or fourth finger respectively. On OKN blocks, participants were instructed to look passively at the middle of the screen (OKN-Block). On Fixation Blocks, participants fixated a central cross (superimposed on the moving background) consisting of a black cross drawn inside a grey circle (RGB: 128, 128, 128). The presentation order of the fifteen OKN and fifteen Fixation blocks was randomized; in each block, 36 targets were equally distributed across location and cue type (no cue, valid cue and invalid cue, see Fig. 1). Eyetracking (see below) was calibrated (10 s) before each block. The effect of exogenous attention was tested on reaction time (RT), accuracy and EEG data using a three-way ANOVA with target direction (left vs still vs right), cue type (valid vs invalid) and block (Fix vs OKN) as within-subjects factors.

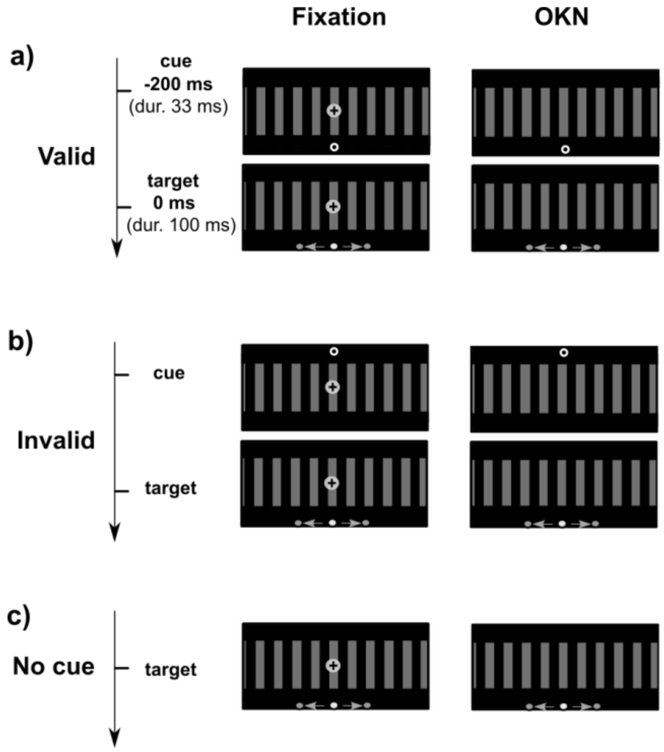

Fig. 1 *Exogenous cuing task during optokinetic stimulation. During both blocks, Fixation (first column) and OKN (second column), bars were moving to the left, visual target stimuli (dots) were presented in either the upper or lower part of the screen. Targets moved left, right or were still. The inter stimulus interval (ISI) between targets onset ranged from 2000 to 5000 ms. Cues (hollow circles) were always presented 200 ms before targets (filled dots, see panel a, b). In the Fixation blocks an additional central fixation point allowed the participants to fixate and suppress OKN.*

EEG acquisition and pre-processing

EEG was recorded continuously at 1000 Hz (BrainAmp DC amplifier, Brain Products, Munich, Germany) from 59 scalp sites using active equidistant electrodes (M72 layout, EASYCAP, Herrsching, Germany). No online filters were applied. Additional electrodes were used for ground (between positions 31 and 1, respectively approximating FPz and FCz in the 10-10 system), reference (ear lobes, active reference on the left) vEOG and hEOG were recorded from two electrodes placed below or lateral to each eye, respectively. Impedance was kept below 10 KΩ. EEG analysis used the EEGLAB Toolbox (Delorme and Makeig 2004). EEG was re-referenced offline to the average of the left and right ear lobes and filtered (notch 50 Hz filter and a Butterworth zero phase filter, bandpass 0.1 Hz to 40 Hz (12 dB/octave, (Luck 2014). Bad channels (mean 6 per participant) were interpolated for figures using a topographic interpolation (spherical spline, order 4). Interpolated channels were not included in the later region of interest analysis. EEG was segmented to 1000 ms before and 2000 ms after target onset. Baseline correction used 1000 ms before target onset. Fast-ICA (Hyvärinen and Oja 2000) was performed to remove the "OKN component" from the EEG signal. OKN components were identified by visual inspection of topographies: due to the specific shape of those reflexive eye movements, a clear OKN component could be found in each participant (see Fig. 2).

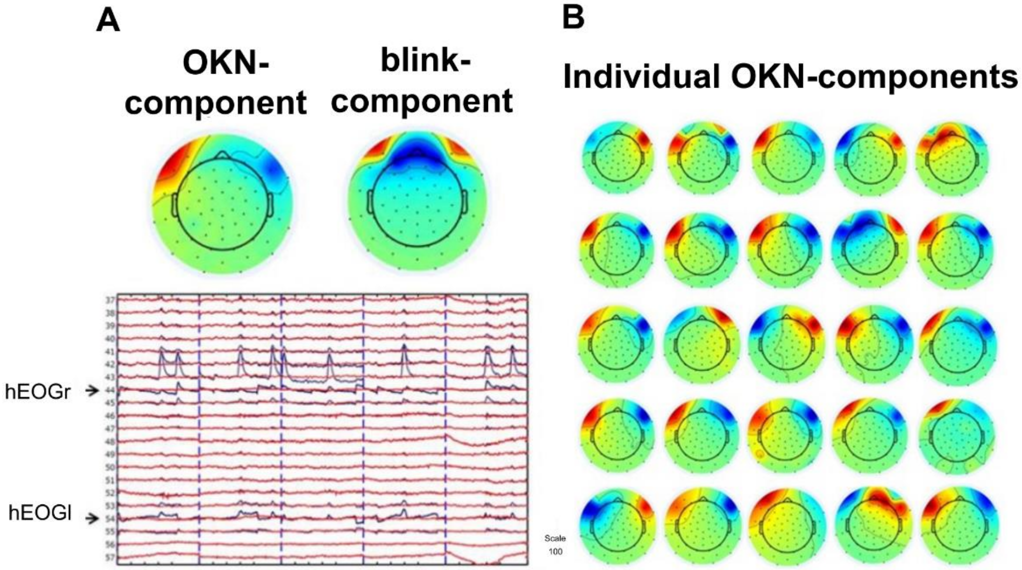

Fig. 2 *Panel A: Topographies of OKN (upper left) and blink (upper right) components identified by ICA, in one representative participant. Lower panel: example of raw data showing the EEG signal before (blue) and after (red) the components detected were removed. Panel B: Map of individual OKN components in the other 25 participants showing the consistency of this component in the EEG signal.*

Event Related Potentials (ERP)

Data were segmented from 100 ms before cue onset until 600 ms after (which was also 400 ms after target onset) and baseline corrected to 100 ms before cue onset. If the peak-to-peak EEG signal exceeded ± 100 µV in any channel, or if the vertical and horizontal EOGs exceeded ± 80 µV, epochs were rejected (Sawaki et al. 2015). A minimum number of 30 trials per condition was established as the criterion to maintain data quality, on our final sample (n = 26), but this criterion was never reached. Upper and lower visual field stimuli were collapsed. In order to reduce the risk of false-positives through multiple comparisons (Luck and Gaspelin 2017) a region of interest (ROI) approach was used, selecting the group of channels showing the largest amplitude at the time of the target-related P1 component on valid still trials, during the Fixation block (80- to 120 ms post-target): this formed a central posterior-left group (positions 4, 11, 12, 25, 39 (red in Fig. 3) corresponding approximately to CPz, Pz, P2, P1, POz, PO3, PO7: see Fig. 3 for all equidistant channel locations overlaid with the standard 10-10 EEG system, two electrodes (13 and 24) were not included in the analysis because they had been interpolated previously).

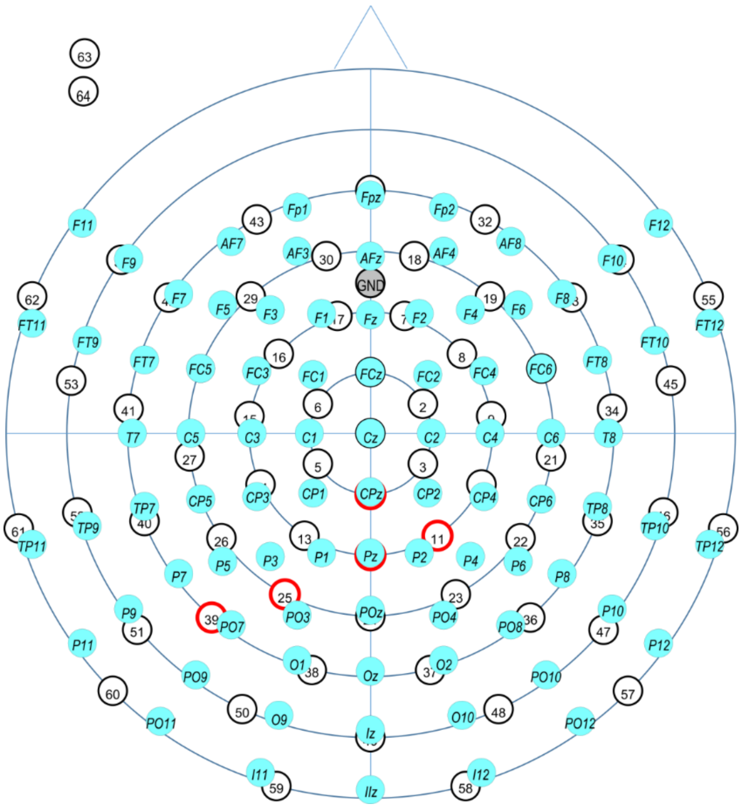

Fig. 3 *Map of equidistant electrodes distribution over the scalp (in white) overlaid with 10-10 international system (in turquoise) for reference. The electrodes showing the largest P1 component, included in the ROI, are indicated with red circles.*

Eye movement recording

Head-mounted video-oculography of the left eye sampled at 220 Hz (EyeSeeCam System, EyeSeeTec, Munich). After blinks (when the signal is lost) were removed, OKN quick phases (QPs) were defined as eye velocity greater than 10 °/s with absolute acceleration greater than 300 $°/s^2$. QP start and end point were defined from the point where the eye velocity peaked, to the point where the eye velocity neared 0°/s. This allowed identifying the QPs in the direction of the OKS. The data were segmented, from 300 ms before cue onset to 300 ms post target onset in order to investigate whether the exogenous cue affected Slow Phase Velocity.

Results

Behavioral results

Reaction time

Attention improved performance of the visual motion discrimination task, even during continuous reflexive eye movements (main effect of cue: $F(1,25 = 52.4$, $P < 0.0001$). This effect of exogenous attention on RTs was independent to target direction and block. There was no significant interactions between target and cue: $F(2,50) = 0.06$, $P > 0.8$; and between cue and block: $F(1,50) = 1.02$, $P > 0.1$); and between all three factors: ($F(2,50) = 2.49$, $P \geq 0.1$). As the attentional effect did not differ between dot motion directions, target directions (left, still, right) were collapsed. This attentional effect was also found within either block separately ($t(25) = -6.05$, $P < 0.0001$) during Fixation, ($t(25) = -6.2$, $P < 0.0001$), and during OKN; Fig. 4. Hence attentional effects on motion discrimination were not found to differ between blocks where participants were moving their eyes or fixating on the moving visual scene. The mean benefit of attention was 24ms and 28ms, for Fixation and OKN respectively. RTs during OKN were generally slower (main effect of block ($F(1,25) = 57.92$, $P < 0.0001$)).

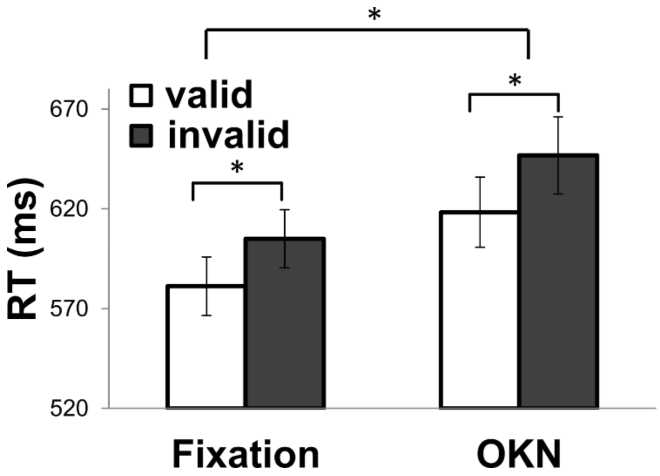

Fig. 4 *Attention affects reaction times during fixation and optokinetic nystagmus.*

Accuracy

As expected, given the different tasks difficulty, performance was better during Fixation compared to OKN (t(25) = 8.3, $P < 0.0001$)Attention did not affect accuracy, nor any interactions between cue and block nor between cue and target direction (all Fs ≤ 2.3, all Ps > 0.1), but a main effect of target direction (F(2,50) = 51.6, $P < 0.0001$) and block (F(1,25) = 68.4, $P < 0.0001$) were found and their interaction (F(2,50) = 39.2, $P < 0.0001$). The analysis on the data combined by target direction revealed no interaction between cue and block (F(1,25) = 0.2, $P > 0.6$).

More correct responses were recorded during valid Fixation (84%) and invalid Fixation (84%) than during valid OKN (71%) and invalid OKN (71%), and the same level of accuracy was registered following valid and invalid cues in both blocks.

Event-related potentials

A target-locked ERP analysis investigated whether a similar attentional effect, i.e. on both Fixation and OKN blocks, was also found at the level of neural activity. The neural activity recorded from the selected ROI and time bin showed the same pattern as the behavioral results: no interaction between cue, block and target direction (all Fs ≤ 2.2, all Ps > 0.1). Once we verified that the exogenous attention was not dependent on visual motion direction, we collapsed the target directions and tested in a two way within-subjects ANOVA. A main effect of cue was found (F(1,25) = 9.73 , P < 0.01), and importantly no main effect of block (F(1,25) = 1.99 , P > 0.3) nor the interaction between the two factors (F(1,25) = 0.69 , P ≥ 0.8). Significant differences between valid and invalid trials was found within each block (t(25) = -2.74, P < 0.05 and t(25) = -2.81, P < 0.05, respectively for Fixation and OKN), where invalid targets elicited a larger P1 component validly cued targets. Highly similar waveforms and effects were observed for Fixation and OKN blocks (see Fig. 5).

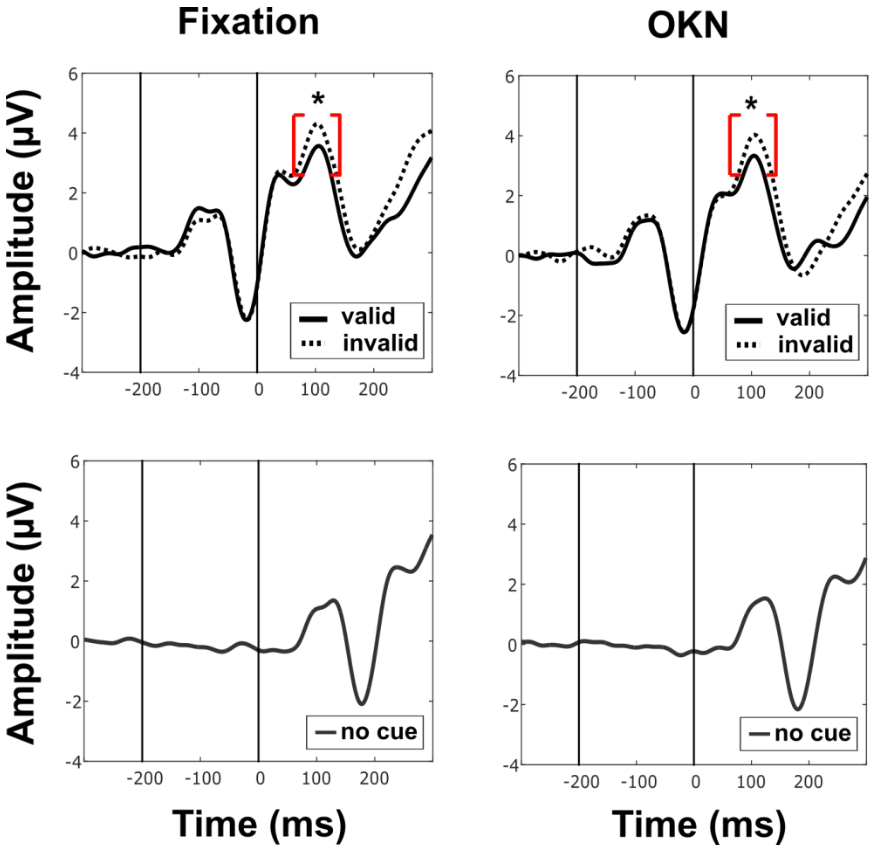

Fig. 5 *Exogenous attention affects the ERP during both Fixation (left panel) and during OKN (right panel). Targets were presented at time zero; valid and invalid targets were preceded by cues at 200 ms before target onset (first row) or without cues ("no- cue", second row). Slow phase velocity of OKN*

Exogenous attention did not affect the oculomotor response during OKN. We derived the SPV differences between 300 ms period after (post) target-onset and a 300 ms period before (pre) cue-onset. As observed at the behavioral and neural level, eye velocities did not differ between target directions (F(2,48) = 0.81, P > 0.4). No interaction between target direction (left vs still vs right) and cue (valid vs invalid) was found (F(2,48) = 0.2, P > 0.8), and so as before target direction was collapsed. There was no effect on the ongoing eye movement velocity after either valid or invalid targets (all P's > 0.05). The effect of exogenous attention was not found in eye movement data; there was no significant difference between valid and invalid trials (t(24) = -0.32, P > 0.7, see Fig.6).

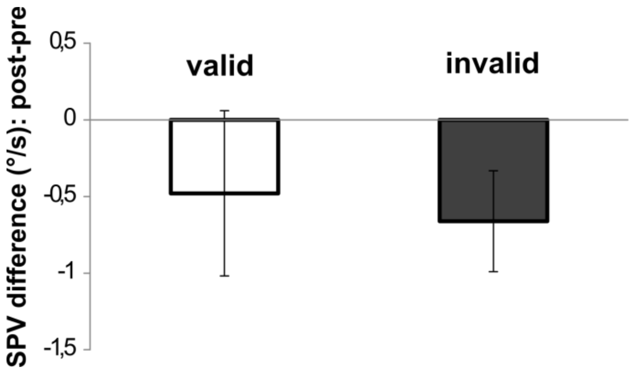

Fig. 6 *Exogenous attention does not change SPV in the visual discrimination task during OKN. The bars represent the difference between post-target and pre-cue SPVs for valid (white bar) and invalid (grey bar) trials.*

Discussion

These results demonstrate that exogenous attention still affects behavior and brain activity even during ongoing reflexive eye movements, with a similar pattern occurring during fixation: here we interpret these findings in the light of previous work on the effects of attention, eye movements, and their relation to clinical and real-world applications.

Behavioral effect of attention

The facilitatory behavioral effect of exogenous orienting to peripheral stimuli has been reported extensively (Yeshurun and Carrasco 1998; Posner 2016). Although it has not previously been demonstrated during optokinetic nystagmus previous work has shown that covert attention can reduce the ability to suppress OKN (Williams et al. 2006b). Additionally, a study combining the Simon effect with OKS showed faster RTs when the response button and the OKS incoming edge were on the same side (Figliozzi et al. 2010). The relationship between overt and covert processing has however been more widely investigated using other types of eye movements. Visual attentional shifts to an upcoming target location precede eye movements in dual-task situations requiring preparing saccades to a specific location and to simultaneously discriminate target features: this pre-saccadic shift of attention has been suggested to be crucial for visual stability (Deubel and Schneider 1996; Rolfs et al. 2011). In addition, perceptual judgments and pursuit eye movements are also modulated by attention, more precise speed change detection occurs in the attended motion direction (Spering and Montagnini 2011a; Spering and Carrasco 2012).

Unlike other studies (Dubois and Collewijn 1979; Gresty and Halmagyi 1979; Williams et al. 2006a; Rubinstein and Abel 2011a; Kanari et al. 2017a), we did not find any attentional modulation on OKN. The reason for this difference might be that the attentional effect was investigated here using exogenous cues which have an effect lasting for a shorter duration than endogenous cues used previously: in addition, the tasks and measures varied across studies.

Slower RTs followed “cue” compared to “no-cue” trials. We speculate that this may have been because the overall presence of a cue (whether valid or invalid) alerted participants leading to them engaging more with the optokinetic stimuli.

Neural effect of attention

Valid and invalid trials showed clear differences starting approximately 100 ms after the target onset on both fixation and nystagmus blocks. This neural correlate of the attentional effect occurred on both block types, further supporting that the OKN eye movement did not prevent the deployment of attention. This effect was at the time of the target-evoked P1 component, which has been suggested to reflect the perceptual processing of stimuli (Mangun et al. 1987; Hopfinger and Mangun 2001). In most previous studies, a larger P1 occurred on valid trials (Hopfinger and Mangun 1998) whereas in this experiment, the P1 ERP components following the dot onset were larger for invalid than for valid targets. Notably other studies that have found the same pattern as here, higher P1 on invalid trials, used situations where the target was difficult to perceive, either because it was low contrast (Chica et al., 2010) or high perceptual load (e.g. Fu et al. 2009; Tan et al. 2015). We therefore speculate that the optokinetic grating present on all trials in our experiment also provided high perceptual load. This posterior P1 modulation has been interpreted as representing feedback from higher order brain region, such as prefrontal cortex, that would be necessary when distractors are presented. As a consequence of this feedback, visuospatial attention enhances the perceptual salience of incongruent stimuli processed in occipital areas (e.g. Tan et al. 2015). The increased P1 in invalid trials has also been interpreted as evidence of early visual areas' modulation in perceptual awareness control (Chica et al. 2010). Note one limitation of this study was the absence of cue-target jittering or cue only trials which could allow methods optimized for segregating out the ERP to cue and target (Woldorff 1993). The pattern of attention reducing P1 may then be related to the presence of the cue-related potential beforehand or to the ongoing background optokinetic stimulation, and future work will be necessary to relate this to previous effects. Independently of this we were here able to show the effect of attention still occurred with or without eye movements.

Clinical and real-world applications

Studies of visual cognition often test for dissociations and interactions between the systems for oculomotor control and for perception. This work often focuses on how we perceive clear "objects" despite performing eye movements (Spering and Carrasco 2015) or whether covert spatial attention is always oriented to the target of eye movements (Jonikaitis and Moore 2019a). In addition, the urge to study brain activity in "natural" contexts is becoming more and more prevailing in neuroscience (Krakauer et al. 2017b; Taylor 2018b). In this study we demonstrated that the classical attentional effect described in several visual attention tasks may not only be confined to the lab but this seems also to be what happens during this experiment's model of the OKN occurring as we explore our environment in the everyday life. The orienting of attention may then play a crucial role in behavior even during the execution of reflexive eye movements in response of moving visual scene, and also in the suppression of those eye movements (the fixation block).

Declarations of interest: none.

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3 General discussion

The present dissertation investigated the perceptual consequences of reflexive eye movements and suppression of those eye movements. This has been done by the stimulation of a brain area involved in oculomotor control and visual perceptual functions, the right frontal eye field (rFEF), and through the manipulation of exogenous attention, in a task measuring perceptual judgments during visual motion discrimination. Below I will briefly summarize the results of the three studies.

3.1 Summary of findings

The first study (Chapter 2.1) tested for a dissociation between oculomotor control and visual perceptual functions of the rFEF, with a task combining OKS and visual motion discrimination. Single-pulse TMS delivered shortly before the target significantly improved the correct discrimination of still targets, despite the ongoing reflexive eye movements generated by OKS. This TMS effect was not observed following leftward or rightward moving targets. Moreover, the perceptual facilitation on still trials was associated with a reduction of the slow phase velocity of the reflexive eye movement response. A dissociable effect of rFEF TMS was found when participants were fixating on a point superimposed upon the moving background: FEF TMS impaired visual perception during the discrimination of contralaterally moving targets. The impaired performance was associated with an abolition of the normal balance of alpha oscillation between frontal and posterior recording sites. A further modulation of rFEF TMS during fixation was observed in the late ERP components reflecting perceptual stimulus evaluation, for still and leftward moving trials. These results offer further evidence of the multifunctionality of this brain region, the rFEF was not only involved in visual perceptual processing during reflexive eye movements but also in the regulation of the oculomotor response to the moving visual scene. rFEF was also critical for maintaining the level of alpha power when the eyes were fixating on the moving visual scene. The second study (Chapter 2.2) investigated the neural correlates of the improved visual perception of still targets following rFEF TMS during reflexive eye movements. This facilitation had not been present during the discrimination of the same stimuli when the eyes were fixating on the moving background. The analysis in the time domain, on TMS-evoked potentials, did not capture a specific modulation for still trials. Nevertheless, the effect registered at the behavioral level was associated with a specific modulation in the alpha domain. Higher level of alpha band power was evident during OKN than fixation, when still targets were discriminated. This TMS task specific effect was not observed after the stimulation of the control site.

The third study (Chapter 2.3) examined the role of exogenous orienting of attention during the novel task developed for the first study. Exogenous attention, implemented by peripheral visual cues that preceded targets, facilitated visual perceptual judgments, measured as response time. Importantly, this exogenous attentional effect occurred during ongoing reflexive eye movements elicited by the visual motion stimulation and also during the suppression of those eye movements. A similar pattern across OKN and fixation was also found at the neural level, where the early P1 component showed a reduced amplitude for valid compared to invalid trials, in both blocks. Orienting of exogenous attention did not affect the oculomotor response elicited by the visual motion stimulation. Based on these findings we can conclude that the orienting of exogenous attention is a process accessible even during the generation of reflexive eye movements and also during the suppression of ocular responses to moving visual scene. Interestingly, the additional attentional orienting did not change the oculomotor response during OKS.

3.2 Frontal eye field: oculomotor control and visual perceptual functions during OKS

An early electrophysiological study described the presence of visual, motor and visuo-motor neurons in the FEF of non-human primates (Bruce and Goldberg 1985). It is known that the FEF is involved in various types of eye movements, in non-human primates as well as in humans, and that its involvement depends on the task executed in the experimental setting (Vernet et al. 2014). Cortical activation of the FEF occurs during saccades, smooth pursuit and OKN, and these three different eye movements activate different sub-regions (Dieterich et al. 2009). The selection of the right FEF and our interest in how its perturbation interfered with the perceptual consequences of reflexive eye movements was based on evidence present in the literature. BOLD signal increases were found in both FEFs during OKN and this was independent from the direction of the visual stimulation (Konen et al. 2005). In addition, it has been suggested that there is a right hemispheric dominance (in right handers) for vestibular cognitive process (Dieterich and Brandt 2015). Additionally, the visual perceptual function of the FEF has been shown in monkeys (Moore and Fallah 2001; Thompson and Schall 1999; Armstrong and Moore 2007) and humans (Grosbras and Paus 2002, 2003; Chanes et al. 2012; Quentin et al. 2013; Bosch et al. 2013) via improved visual performance after FEF stimulation. In a previous study that also used an online TMS protocol, like the one we used, single-pulse TMS delivered shortly before target onset decreased the visual perceptual threshold, and thereby improved the detection of the target location. This TMS effect occurred independently from the visual field where the target was presented but only following the stimulation of right FEF, whereas the effect of left FEF TMS was limited to targets presented within the contralateral visual field (Grosbras and Paus 2003). These findings together with the suggested specialization of the right hemisphere in higher vestibular functions and the absence of a direction preference of FEFs during OKS, led to our decision of focusing on the causal role of the right FEF in dealing with perceptual consequences of OKN.

The work described here extends the role of the FEF in visual stability into the domain of the slow eye movements occurring during optokinetic stimulation. It has to be noted that by "visual stability" we refer to the preservation of accurate visual perception on nearby objects (Angelaki and Hess 2005). TMS studies on humans showed that the FEF is crucial for deviating saccades away from the distractor, during tasks where the target and the distractor were simultaneously presented (Walker et al. 2009; Bosch et al. 2013a). The findings presented in this dissertation showed that stimulation of the FEF not only improved visual stability, in terms of correct discrimination of still stimuli, but also reduced the slow phase velocity of the OKN. The link between FEF and visual stability has often been explored solely via the corollary discharge that can act as a cue for visual stability (Moore and Armstrong, 2003; Moore and Fallah, 2004). By contrast the work here has looked at visual reafference, focusing on visual cues received from the motion of the visual scene. Visual reafference, together with proprioception and corollary discharge, are the three signals used for visual stability (Wurtz 2008). The mechanism that produces visual stability during slow eye movements and fast eye movements, like saccades, might be very different: in fact saccades are so fast that visual input during the eye movement is blurred and is even suppressed (Bridgeman 2011).

The present thesis suggests that cortical cognitive mechanisms seem to be responsible for dealing with the perceptual consequences of the subcortical OKN. Stimulation of the FEF modulated visual perception in an opposite way during OKN and suppression of OKN, producing facilitatory and inhibitory effects, respectively. The different types of neurons found in the FEF support multifunctionality of this brain region (Schall 2002; Joiner et al. 2013; Chen et al. 2018). Our behavioral results were supported by a specific change of the alpha oscillations induced by TMS, and it has been previously suggested that stimulation of FEF modulates responses in posterior visual cortex (Ruff et al. 2006; Silvanto et al. 2006; Taylor et al. 2006; Cocchi et al. 2016), and in particular right FEF TMS might perturb the connection between frontal and posterior sites (Sauseng et al. 2011). In fixation blocks, when participants were fixating with a moving background, the impaired visual performance for contralateral motion discrimination was associated with an abolition of the balance of alpha oscillations (by rFEF TMS) across frontal and posterior sites, whereas in conditions where no TMS effect had been recorded at the behavioral level, the normal alpha band balance between the two regions was observed. Attention modulates alpha oscillations (Thut et al. 2006), and moreover attention is also important to control the level of alpha in order to process irrelevant information (Händel et al. 2011). We suggest that this mechanism might be supporting the discrimination of still stimuli during ongoing reflexive eye movements, and the effect on still trials was found only during OKN and not during fixation in our experiment. The alpha power induced by rFEF TMS, when compared between blocks, showed that the increase in accuracy for discrimination of still targets was associated with a higher level of alpha during OKN than during fixation. The perception of still targets was updated on the basis of the moving visual scene (visual reafference) and this required a higher level of alpha in order to ignore the moving background to the benefit of visual discrimination of the target. This did not occur during fixation, because of the absence of the retinal slip needed to stabilize visual image on the retina, which instead occurred during OKN.

3.3 Covert orienting of attention during reflexive eye movements

Attentional orienting has been investigated in association with fast eye movements but very little it is known about the link between covert attention and slow reflexive eye movements. We have contributed in filling in this gap by examining the modulation of exogenous attention on visual motion discrimination during OKN, here following the presentation of valid or invalid cues (instead of stimulation of the rFEF). Indeed we know from behavioral and neural evidence that the FEF stimulation is likely to mimic an attentional signal (Moore and Fallah 2001; Armstrong and Moore 2007). Visual attention affects OKN (Williams et al. 2016; Rubinstein and Larry 2011; Kanari et al. 2017). Attention may also affect the suppression of nystagmus. The optokinetic nystagmus can be suppressed in the presence of a stationary object, such as the fixation point during optokinetic stimulation (Ter Braak 1936; Murasugi et al. 1986) or an attended afterimage (Howard et al. 1989). Weaker suppression occurred when participants were instructed to attend away from the fixation point during nystagmus suppression (Williams et al. 2006). These findings seem to be relevant for our first study and we could speculate that the stimulation of rFEF might have oriented the attention to still dot targets in spite of the ongoing reflexive eye movements. The second study investigated more closely the putative attentional mechanisms behind our novel task.

To our knowledge there is no other study that investigated the manipulation of exogenous attention in visual motion discrimination task during passive viewing of moving visual scenes and during the suppression of the moving visual scene. Importantly, our findings extend the behavioral and neural signatures of exogenous attention (well reported in the literature), to a situation where visual motion discrimination is combined with reflexive eye movements. The facilitatory effect of exogenous orienting to peripheral stimuli replicated in our study has been extensively described (Yeshurun and Carrasco 1998; Posner 2016). In our task a constant time interval of 200 ms between cue onset and target onset lead to the facilitation of the RTs following valid compared to invalid trials, and this exogenous attentional effect was observed despite the continuous reflexive eye movements. The involuntary orienting of attention rises and decays rapidly: this transient attention has a peak at about 100-120 ms (Müller and Findlay 1987; Remington et al. 1992; Ling and Carrasco 2006; Liu et al. 2007). Several ERP components modulated by exogenous and endogenous (or voluntary) attentional orienting have been investigated in previous studies. We focused on the early P1 component, as this component has been suggested to reflect the perceptual processing of stimuli (Mangun et al. 1987; Hopfinger and Mangun 2001). Despite reflexive ongoing eye movements and the suppression of those eye movements, we have successfully found in our data the typical neural correlates often described with exogenous attention. P1 modulations have been reported when attention was oriented exogenously by peripheral cues, and the stimulus onset asynchrony (SOA) has been described as crucial to influence the amplitude of this early component: a larger P1 was associated with cued compared to uncued location with short SOAs (Hopfinger and Mangun 1998) whereas a smaller P1 was elicited using longer SOAs (Prime and Ward 2006; Tian and Yao 2008). Although in our study we have used a short SOA, the P1 ERP component following dot onset was larger for invalid than for valid targets. Other studies have found this similar modulation (e.g. Fu et al. 2009; Tan et al. 2015). The posterior P1 modulation has been interpreted in studies using working memory tasks as reflecting feedback from higher order brain region, such as prefrontal cortex, that would occur when distractors are presented. Visuo-spatial attention can boost the perceptual salience of incongruent stimuli processed in occipital areas (e.g. Tan et al. 2015), as a consequence of this feedback mechanism. An increased P1 in invalid trials has also been associated with the modulation of early visual areas for perceptual awareness (Chica et al.

2010). The larger response on invalid trials could be due to the alerting effect provoked by reorienting attention in spatially incongruent trials, for example when cues are presented at the opposite location of impending targets. Likewise in our data, despite the use of a different task, P1 amplitude was larger for invalid than for valid targets, and we could speculate that the presence of an optokinetic grating throughout our experiment contributed to a high perceptual load. The increased response registered in the parieto-occipital regions might then be interpreted as a result of the exogenous orienting of attention engaged by invalid targets to their locations. In fact, P1 modulation might indicate feedback from higher order brain region, such as prefrontal cortex, that would be necessary when distractors, invalid cues in our experiment, are presented. The fronto-parietal network, often described as responsible for attentional mechanisms (Corbetta and Shulman 2002; Fox et al. 2006), is not the only one to be involved in attentional processes (Chica et al. 2013). Human and animal studies have revealed attentional modulation in occipital cortex (Gandhi et al. 1999; Wang et al. 2015).

Differently from what was observed in other studies (Williams et al. 2006; Rubinstein and Abel 2011; Kanari et al. 2017; Dubois and Collewijn 1979; Gresty and Halmagyi 1979), we did not find an attentional modulation on OKN. One of the reasons for this difference might be that the attentional effect was investigated on different features of nystagmus, like frequency and gain, and another reason might be that different tasks were used. For example in Kanari et al. (2017), two motion stimuli, patterns of moving dots inducing OKN, were presented either on the sides of a fixation cross or above or below it; a visual cue indicated which of the two moving stimuli participants had to attend to. The frequency and the gain (ratio of the slow phase velocity to stimulus velocity) of OKN increased when the moving pattern in the peripheral visual field was the focus of attention. In our task we could not find any specific attentional modulation on SPVs: eye velocities were unchanged between valid and invalid trials. Despite our finding we cannot exclude an involvement of exogenous attention during reflexive eye movements, importantly the task used was not designed to be sensitive to eye movement changes but rather to the visual perceptual consequences of those eye movements. Visual and oculomotor signals have been described as being integrated in order to select a visual target, and the preparation of saccades, largely investigated, seems to play a crucial role in orienting covert spatial attention (Awh et al. 2006; Rolfs et al. 2011). Other studies have shown that slow eye movements such as smooth pursuit can be perturbed by different visual background (Spering and Gegenfurtner 2007; Haarmeier and Kammer 2010; Spering and Montagnini 2011b). The OKN system, despite its involuntary nature, is coordinated with other systems: planned saccades compensated for their displacement due to nystagmus showing a relationship between reflexive and volitional systems (Harrison et al. 2015). Early investigations as to the shared attentional mechanism between slow eye movements and perception led to the conclusion that improved perception in a visual search task during pursuit was associated with a small change in eye velocity (Khurana and Kowler 1987). Slow eye movements and in general reflexive eye movements, as our findings show, might not provide attentional external indicators.

3.4 Real world and clinical implications

The work described in this dissertation attempted to answer a more general question, namely how do we tackle the challenges to visual perception generated by the fact that our eyes are never stationary when we move in our environment. We know that these continuous reflexive eye movements are generated in order to stabilize a clear visual image on the retina. Interestingly, based on our findings now we also know that higher brain area and attentional mechanisms are also playing an important role.

This work focused on cognitive aspects and regions in the brain involved in the complex mechanisms behind how we perceive clear "objects" despite performing eye movements (Spering and Carrasco 2015). In the last decades, studies of visual cognition have investigated the dissociation and interaction between systems responsible for oculomotor control and for perception. Eye movements and attention were explored in order to understand whether those systems were working interactively or were instead working in parallel. The majority of studies have reported an overlap between brain structures that support eye movements and spatial attention (e.g. Grosbras et al. 2005). Visual cortical activity is modulated by the oculomotor control areas and those areas are causally engaged in spatial attention (Lovejoy and Krauzlis 2010; Bollimunta et al. 2018; Jonikaitis and Moore 2019b). Most of the relevant studies present in the literature tested those two systems, attention and eye movement, with cognitive tasks that are unlike to what can be experienced in everyday life situations. The link between those mechanisms has been here explored and observed during an experimental situation where we were not measuring perceptual performance during the execution of a limited amount of eye movements (unlikely situation in the real world), but rather perceptual judgments were required during the generation of continuous reflexive eye movements, providing a situation more similar to a natural visual scene. As emphasized recently across the community of neuroscience there is an urge to study brain activity in "natural" contexts (Krakauer et al. 2017a; Taylor 2018a). The development of experimental settings that allow the investigation of behavioral and brain responses to "more natural tasks" will prepare us to deal with the understanding of the cognitive mechanisms of the human brain in its natural environment. The findings reported throughout this dissertation show that the modulation of activity in parieto-occipital regions induced by higher brain areas, such as the FEF, and the consequent influence of this perturbation on the behavioral response, may not be limited to a conventional fixating lab setting. As well as the typical attentional orienting mechanism observed during the generation of reflexive eye movements, and also during their suppression, it may be that this is what occurs when we navigate our environment, and when perceptual judgements are made in spite of oculomotor responses to the optic flow that we experience continuously.

The clear involvement of the right FEF and exogenous attention in dealing with the perceptual consequences of reflexive eye movements could also add important knowledge in the understanding of mechanisms behind a specific clinical situation where damaged visual perception and abnormal involuntary eye movements coexist. Impaired visual perception may follow vestibular lesions, occurring as “oscillopsia”, a clinical condition characterized by blurred vision. Oscillopsia adaptation after vestibular failure might be controlled by central cortical mechanisms through downregulation of visual areas’ excitability, reducing the symptoms due to excessive eye movements (Shallo-Hoffmann and Bronstein 2003; Ahmad et al. 2017b). Here we have demonstrated that when healthy controls had to discriminate the motion direction of stimuli presented during visually driven eye movements, the influence of the right FEF over the visual cortex led to an improvement at visual perception accompanied by a reduction in eye movement velocity. Based on these results we could speculate that a brain region such as the FEF, characterized by its oculomotor control and visual perceptual functions, might be playing a crucial role also in clinical conditions, such as oscillopsia, where perceptual consequences of abnormal eye movements, such as nystagmus, need to be resolved. Of course further investigations could confirm this; it would be interesting to explore the effect of FEF TMS during a visual perceptual task on patients affected by pathological nystagmus. Not only might the stimulation of the FEF, but also the manipulation of attention, be important to understand the damage of higher vestibular functions that follow vestibular lesions. Covert attention orienting to a specific location in the visual field activates the retinotopic visual cortex (Kastner et al. 1999) and deactivates signals representing other locations outside of the attentional focus (Smith et al. 2000). These attentional mechanisms might be crucial to comprehend the cognitive consequences of vestibular lesions and perhaps to develop treatments directed to alleviate the symptoms of clinical condition such as oscillopsia.

3.5 Conclusion and future works

Taking together the findings described throughout this dissertation, a contribution has been made in the understanding of the cognitive mechanisms behind the perceptual consequences of reflexive eye movements. Thanks to the multi-modal approach, and a task developed in order to dissociate visual perception and action (eye movements), we demonstrated that specific brain areas and cognitive mechanisms are engaged when perceptual judgements need to be made in spite of reflexive eye movements. We attempted to bring into the lab context a situation that can be easily generalized with the everyday life situations where perceptual judgments are always combined with eye movements.

Following these results a multifunctional role of the right FEF is inferred, and indeed the right FEF TMS led to two dissociable effects depending on the task that participants were performing. Visual performance for still targets was facilitated during OKN whereas visual performance for contralateral moving stimuli was reduced during the suppression of OKN. The behavioral findings cannot be explained by a potential motion adaptation process during continuous optokinetic stimulation, rFEF TMS has direction specific effects, moreover, the control group, despite the use of the same visual stimulation did not show the same results. As described in the previous sections, these behavioral effects were consistent with the brain activity response and the oculomotor control response. One limitation of this study is that it remains an open question whether these results are selective to the brain area selected, or whether similar effects could be found stimulating a different cortical region involved in eye movements, for example the parietal eye field. The TMS pattern of effects found in this study may be restricted to the design and choice of control site used here, where there were no effects, and to the background motion direction or speed.

In these studies, the speed of the moving background was kept constant as it was crucial for us to measure target dot perception relative to the visual reference frame (OKS). The current aim was not to perturb the optokinetic response per se, which is primarily controlled by circuits in the brainstem and cerebellum (e.g. Ruehl et al. 2017; Gulyás et al., 2006; Hoffmann et al., 2004). The common purpose of the described studies was to demonstrate the relevance of the FEF and covert attention in maintaining visual stability during OKS through compensating for the perceptual consequences of those eye movements.

In the study investigating the manipulation of exogenous attention, we showed that the same attentional effect is still occurring during ongoing reflexive eye movements and also during the suppression of those eye movements. This effect indicated that unlike the role of the right FEF, the facilitatory effect of exogenous orienting of attention is not specific for a visually driven eye movement context but attention facilitated visual perception also during suppression of ocular responses to the moving visual scene (fixation). The neural correlates of these effects, measured as the reduction of P1 amplitudes, may be related to the presence of the cue-related potential or to the ongoing visual motion discrimination (optokinetic stimulation), and future studies will tell if this was related to the presented effects.

We conclude that a multi-modal approach, combined with a task like the one developed for these studies, might be powerful for addressing relevant scientific questions geared towards the understanding of healthy and damaged cognitive mechanisms in contexts closer to a “natural” setting.

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