Cerebral Cortex Advance Access published June 24, 2011

Cerebral Cortex
doi:10.1093/cercor/bhr143

Theta-Burst Stimulation over Human Frontal Cortex Distorts Perceptual Stability across Eye Movements

Florian Ostendorf, Juliane Kilias and Christoph J. Ploner

Department of Neurology, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

Address correspondence to Florian Ostendorf, Department of Neurology, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. Email: florian.ostendorf@charite.de.

We perceive a stable outside world despite the constant changes of visual input induced by our eye movements. Internal monitoring of a corollary discharge associated with oculomotor commands may help to anticipate the perceptual consequences of impending eye movements. The primate frontal eye fields have repeatedly been presumed to participate in the maintenance of perceptual stability across eye movements. However, a direct link between integrity of frontal oculomotor areas and perceptual stability is missing so far. Here, we show that transcranial magnetic stimulation (TMS) over the right human frontal cortex impairs the integration of visual space across eye movements. We asked 9 healthy subjects to report the direction of transsaccadic stimulus displacements and applied TMS before the actual experiment in a novel offline stimulation protocol, continuous theta-burst stimulation (cTBS). A systematic perceptual distortion was observed after stimulation over the right frontal cortex that was best explained by an internal underestimation of executed eye movement amplitudes. cTBS apparently disturbed an internal prediction process for contraversive saccades, while the metrics of associated oculomotor actions remained unchanged. Our findings suggest an important role of the frontal cortex in the internal monitoring of oculomotor actions for the perceptual integration of space across eye movements.

Keywords: corollary discharge, efference copy, frontal eye fields, saccades, transcranial magnetic stimulation

Introduction

Internal monitoring signals could represent a general and efficient means to distinguish self-induced from external changes in our sensory experience. A corollary discharge (CD) associated with motor commands may be used to cancel the reafferent sensory consequences of evoked movements. Perceptual attenuation by CD-mediated sensory gating has been described for various species and different sensorimotor modalities (Crapse and Sommer 2008a) and may help to dampen the visual blur associated with fast saccadic eye movements (Burr et al. 1982; Thiele et al. 2002). However, integrating the displaced visual information before and after saccadic eye movements into a coherent percept requires a spatially more explicit mechanism beyond global sensory attenuation.

Neurophysiological studies identified a possible candidate mechanism mediating the transsaccadic integration of visual space. Receptive fields of visually responsive neurons in the frontal eye fields (FEFs) (Umeno and Goldberg 1997; Sommer and Wurtz 2006), the posterior parietal cortex (Duhamel, Colby, et al. 1992; Medendorp et al. 2003; Merriam et al. 2003), and earlier visual areas (Nakamura and Colby 2002) have been shown to shift their retinotopic location before an impending eye movement. This predictive remapping could help to anticipate the perceptual consequences of eye movements and may partially be driven by CD signals projected back from brainstem structures (Sommer and Wurtz 2002, 2006). Different lines of evidence support a causal role of parietal cortices in transsaccadic space integration: Patients with parietal lesions have been shown to exhibit deficits in an oculomotor double-step task that requires CD for correct execution of a saccade sequence (Duhamel, Goldberg, et al. 1992; Heide et al. 1995). Furthermore, recent studies successfully applied transcranial magnetic stimulation (TMS) over parietal regions to interfere with transsaccadic space integration in oculomotor (Morris et al. 2007), perceptual (Chang and Ro 2007), and memory (Prime et al. 2008) tasks.

Somehow surprisingly, the consequences arising from disturbances in frontal predictive remapping circuits have remained obscure: In patients with cortical lesions affecting the FEF, no clear evidence for impaired updating in a double-step task could be obtained (Rivaud et al. 1994; Heide et al. 1995). However, additional oculomotor deficits (Rivaud et al. 1994; Heide et al. 1995) and mechanisms of plasticity with permanent FEF lesions (Schiller et al. 1979) may impede the demonstration of updating impairments in these patients. TMS over FEF has been shown to modulate feedback signals to earlier visual areas (Ruff et al. 2006; Taylor et al. 2007), without necessarily affecting oculomotor actions (Müri et al. 1991; Ro et al. 1997). These findings may render TMS a suitable tool for interference with frontal remapping mechanisms. To our knowledge, only one recent study pursued this approach and showed that single-pulse TMS over FEF disrupted visuospatial short-term memory for multiple objects (Prime et al. 2010). Since memory disruption was more pronounced when an intervening saccade was required, interference with spatial updating mechanisms was proposed to account for the observed impairment.

In the present study, we used TMS to study a possible role of the human FEF for transsaccadic integration of visual space. Displacing visual information within a saccade can serve as an experimental probe for transsaccadic space integration: Due to saccadic suppression (Burr et al. 1982), observers cannot make use of motion cues to report the displacement direction after saccade completion. In conditions without further visual references, successful displacement detection requires the integration of reafferent visual information with an internal estimate of the executed saccade. In this task, target displacements that are easily detected under fixation conditions can escape a subject's perceptual awareness, a phenomenon known as saccadic suppression of displacement (SSD; Bridgeman et al. 1975). However, a small experimental manipulation has been shown to strongly improve perceptual performance: When the visual target is temporarily switched off within the saccade and reappears after a brief blank period following saccade execution, subjects are able to report target displacements with much higher sensitivity that can even exceed performance under steady fixation (Deubel et al. 1996). Apparently, in this task variant, subjects can make efficient use of accurate and precise CD information, conveying internal information about the executed saccade (Deubel et al. 1996; Ostendorf et al. 2010). We reasoned that this task variant might serve as a sensitive probe to measure putative alterations in transsaccadic space integration induced by TMS.

Materials and Methods

Participants

Nine healthy right-handed subjects (4 female; mean age, 29 years) participated in the experiment. All subjects had normal or corrected-to-normal vision and gave written informed consent before participation. Subjects were free from any contraindications to TMS, as assessed by a screening questionnaire before participation in this study (Keel et al. 2001). All but one subject were naive with respect to the purpose of the study that was approved by the local ethics committee (Charité—Universitätsmedizin Berlin, Germany) and conducted in conformity with the Declaration of Helsinki.

Experimental Setup

Subjects sat at a viewing distance of 50 cm in front of a 22-inch CRT-monitor (refresh rate, 120 Hz) with their heads stabilized by a chinrest and a bite bar. Eye movements were recorded with high-speed video-oculography (sampling rate, 500 Hz; iView X Hi-Speed PRIMATE system, Sensomotoric Instruments, Teltow, Germany). Experiments were carried out in an otherwise darkened room. Subjects completed the experiments in multiple test sessions on different days. All stimuli were white (luminance, 55 Cd/m^2) and presented on a homogenous gray background (luminance, 14 Cd/m^2). A relatively high background luminance was chosen to exclude any spurious effects of phosphor persistence. Previous work demonstrated that visible screen borders should not influence localization with our stimulus configuration (Deubel 2004). Nevertheless, if stationary references would have influenced the present results, they should have dampened any differential effect between conditions. Visual presentation was realized by using Matlab (The Mathworks, Natick, MA) and Cogent Graphics (Wellcome Department of Imaging Neuroscience, University College London, UK).

TMS Protocol

TMS was delivered using a Magstim Rapid^2 stimulator (The Magstim Company, Whitland, UK) and a 70-mm figure-of-eight coil. Offline TMS was used in a continuous theta-burst stimulation (cTBS) protocol as one stimulus train with 200 bursts (3 pulses at 30 Hz with an interburst interval of 100 ms; approximate train duration, 33 s). This specific cTBS protocol has been reported to be effective for FEF stimulation (Nyffeler et al. 2006).

Stimulation intensity for the cTBS protocol for each subject was determined relative to the individual motor threshold (MT). For the determination of MT, the hand area of the right motor cortex was localized as the optimal site for evoking visible motor twitches from the first dorsal interosseus muscle of the left hand. TMS intensity was adjusted until visible motor twitches were elicited in 5 of 10 trials during weak opposition of the left thumb and index finger and this intensity setting was defined as the individual MT. cTBS was administered at 80% of individual MT (Huang et al. 2005; Nyffeler et al. 2006) (mean resulting intensity relative to maximum stimulator output, 41%). Subjects were asked to keep their eyes closed during cTBS administration.

For FEF stimulation, the axis of the coil was angled at 90° from the sagittal axis (with the handle pointing laterally). To control for unspecific stimulation effects, we used the vertex as a control stimulation site in a second cTBS condition (with the vertex localized as Cz according to the EEG 10–20 system and the coil handle pointing backward). TMS for both stimulation sites and stimulation protocols was administered with the coil held in position by a mechanical arm (MagicArm, Manfrotto, Bassano Del Grappa, Italy) and subjects' heads rigidly stabilized as described above. Earplugs were provided to dampen the noise associated with coil discharge. None of our subjects reported any side effects due to cTBS.

Localization of the Right FEF Region

We localized the FEF region to a position 2 cm anterior to the hand area. This relative localization method has been used successfully in previous reports (e.g., Ro et al. 1999; Nyffeler et al. 2006) and should place the stimulation site close to the junction of the precentral sulcus and the superior frontal sulcus (Paus 1996). To further verify correct positioning over the putative FEF region, we used a simple oculomotor task as a functional marker (Grosbras and Paus 2002; Taylor et al. 2007). In this task, we took advantage of the finding (Müri et al. 1991; Ro et al. 1997) that TMS shortly before voluntary nonreflexive eye movements delays contraversive saccades.

In the functional marker task, 2 square boxes (extent, 0.94°) were presented at 10° eccentricity left and right from a central fixation cross (extent, 0.5°). After a variable foreperiod (1400–2000 ms), the central fixation cross transiently changed into a filled square (extent, 0.5°) for 100 ms which served as a central go-signal to execute a saccade to the left-sided box as fast and accurate as possible. Each experimental block started with 12 trials without TMS that were followed by a short notice announcing stimulation start. For the rest of the block, 16 trials with TMS and 16 trials without stimulation were presented in random order. The computer running the visual presentation controlled timing of TMS pulses. The software algorithm aimed at triggering a TMS pulse 50 ms before the expected saccade onset (Grosbras and Paus 2002) as estimated by a running median from the previous nonstimulated trials in an experimental block. The initial site was accepted as putative FEF region if a significant prolongation of contraversive saccadic reaction times (SRT) was observed (as assessed online by Mann–Whitney U tests with a statistical criterion of $P < 0.05$). In the absence of a significant SRT prolongation, we adjusted coil positioning to a new site in 0.5 cm steps with reference to a grid drawn on the scull surface with grease pencil. In the majority of cases (56%), the first site tested was effective and we needed on average one site adjustment (range, 1–4; maximum distance to initial stimulation site, 1 cm) before we obtained a significant SRT prolongation. We confirmed a significant SRT prolongation by offline analysis of eye movement data (Wilcoxon test, $P < 0.004$; median SRT prolongation, 35 ms or 18% compared with baseline SRT). The size of the effect closely corresponds to a previous report using a similar functional marker task (Grosbras and Paus 2002).

Mean scalp coordinates of the functionally characterized putative FEF region were 18 mm (range 15–20 mm) anterior and 2 mm (range 0–10 mm) lateral to the hand motor area as characterized above. These coordinates are consistent with previous reports (Ro et al. 1999; Nyffeler et al. 2006) and a meta-analysis on the relative anatomical topography of the FEF relative to the hand motor area, as characterized by functional neuroimaging (Paus 1996). We evaluated the anatomical position of the functionally characterized FEF in 2 of our subjects by post hoc coregistration of the individual stimulation site to individual high-resolution magnetic resonance imaging scans (3 T, 1 mm isotropic resolution), using the eXimia system (Nexstim, Helsinki, Finland). This system utilizes optical tracking of subject's head position and coil position together with individual structural MRI and a spherical head model to estimate the cortical stimulation site and strength. In both subjects, the stimulation site was located near the posterior end of the middle frontal gyrus, rostral, and slightly lateral to the junction of the precentral and superior frontal sulcus (Supplementary Fig. S1). To determine stereotactic coordinates of the stimulation site, individual MRI data sets were normalized by using the unified segmentation and normalization function provided with SPM 5 (Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm). Average Talairach coordinates of stimulation sites were $x = 31$, $y = 2$, $z = 50$, closely corresponding to the putative location of the human FEF (Paus 1996).

Transsaccadic Displacement Detection—The Blanking Task

A fixation cross (extent, 0.5°) was presented at screen center. After a variable foreperiod (1600–2400 ms), the fixation cross was switched off and a target cue for a saccadic eye movement (diameter, 0.5°) was simultaneously presented randomly at either the right or left side of the screen at 8° or 10° eccentricity, respectively (see Fig. 1*A*). Triggered by saccade onset, this target was switched off during saccade execution (median delay after saccade onset, 16 ms) and reappeared after a temporal gap of 250 ms at an unpredictable position. We introduced a temporal gap before target reappearance since this experimental manipulation has been shown to increase the sensitivity for transsaccadic stimulus displacements (Deubel et al. 1996; Ostendorf et al. 2010). Target displacement for a given trial was adapted by 3 independent randomly interleaved staircases with a constant step size of 1°, separately for right and left saccade direction. Specifically, when the subject indicated a target displacement to the left for a given displacement level, the next probe for a given staircase would be shifted by 1° to the right. Staircases started at a displacement level of 2.33° right- and leftwards and 0° (no displacement) with respect to initial target position. Subjects reported the apparent jump direction by pressing the right or left button of a computer mouse. Subjects were instructed to always press a button, corresponding to the more likely displacement direction. Response registration was limited to maximally 5 s after target onset.

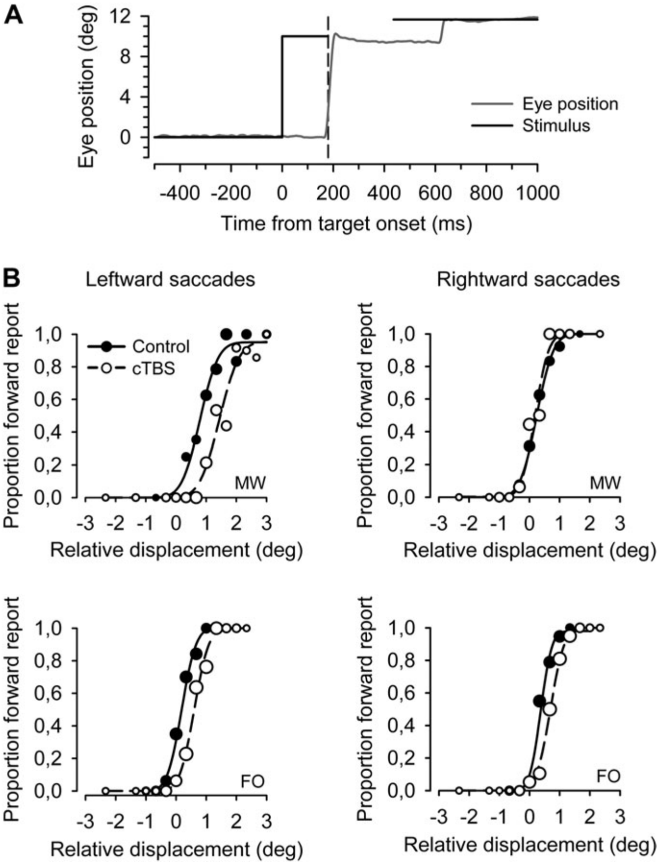

Figure 1. Schematic of blanking task (*A*). A peripheral target was presented right or left of screen center simultaneously with the disappearance of a central fixation cross (black line). Subjects followed with a saccadic eye movement (exemplary eye trace in horizontal dimension, gray line). The eye movement triggered a saccade-contingent stimulus change (time-point indicated by vertical dashed line): The target disappeared for 250 ms and then reappeared at a displaced position. Note the occurrence of a secondary saccade that corrects for the artificially induced targeting error of primary saccade. (*B*) Psychometric functions for 2 sample subjects (MW and FO) in a control condition without prior stimulation (Control, black circles and continuous lines) and in a condition with prior theta-burst stimulation over FEF (cTBS, white circles and dashed lines). Circles denote proportion of trials in which subjects reported an apparent stimulus jump in saccade direction (forward), plotted against relative displacement level. Negative values refer to target displacements against saccade direction. Circle sizes represent the number of trials for a given target jump. Cumulative gaussians were fitted to perceptual response data separately for leftward and rightward saccades.

Behavioral effects after a single train of cTBS have been described to last for approximately 30–60 min (Huang et al. 2005; Nyffeler et al. 2006). We therefore decided to probe transsaccadic displacement detection with sessions lasting up to 30 min, immediately following cTBS administration (actual average session duration following cTBS over FEF was 28 min). This allowed for the completion of 9–12 blocks (24 trials each) per subject. A comparable number of trials were collected for the control condition without any TMS.

Fixation Task

The "Fixation Task" employed physically identical stimuli as the "Blanking Task", but subjects were now instructed to keep fixating on screen center when the fixation cross was switched off and the peripheral target appeared (see Fig. 2*A*). The peripheral target was switched off after a constant time period of 180 ms and then reappeared after a temporal gap of 250 ms at an unpredictable position. Trials were aborted online and repeated immediately if eye position left a circular area of ~2° radius around screen center. During offline analysis, we checked for fixation maintenance with a more stringent criterion and excluded any trials in which small saccades (minimum

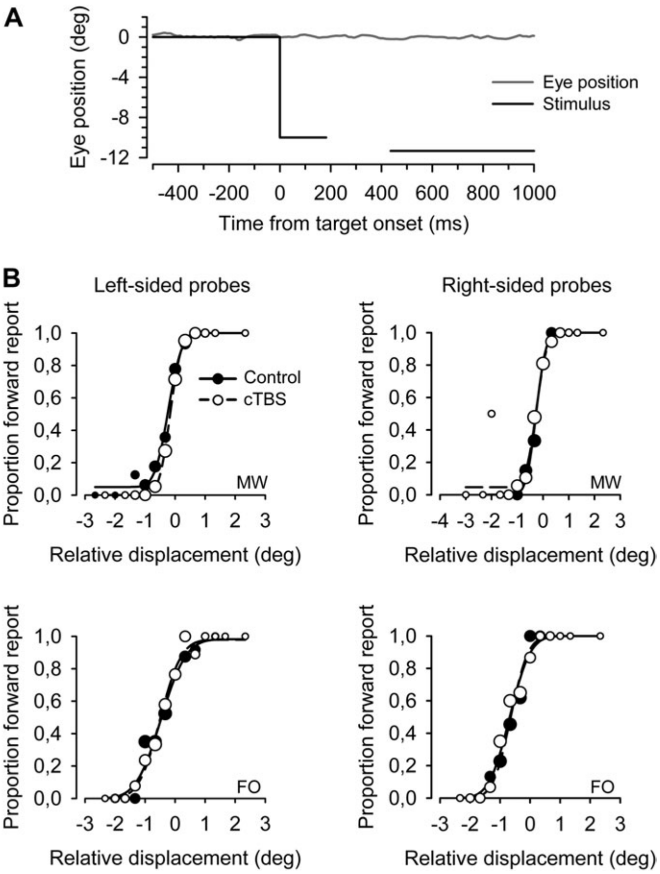

Figure 2. Schematic of fixation task (*A*). Visual stimuli (black line) were identical to the blanking task. However, subjects were instructed to maintain fixation at screen center after disappearance of the central fixation cross (eye trace in horizontal dimension, gray line). The peripheral target was presented for 180 ms, disappeared for 250 ms, and then reappeared at a displaced position. (*B*) Psychometric functions for 2 sample subjects (MW and FO) in a control condition without prior stimulation (Control, black circles and continuous lines) and in a condition with prior cTBS over FEF (cTBS, white circles and dashed lines). Figure conventions otherwise follow Figure 1*B*.

amplitude, 0.5°) had occurred before the displaced target reappeared (mean exclusion rate, 5%).

Displacement Detection with Online Single-Pulse TMS

Offline TMS with cTBS is a relatively novel stimulation protocol (Huang et al. 2005; Nyffeler et al. 2006) that appears to affect cortical processing in a differential manner (Stagg et al. 2009; Cárdenas-Morales et al. 2010) compared with single-pulse TMS (Walsh and Cowey 2000). Since earlier studies mainly used online TMS to interfere with nonoculomotor FEF functions (e.g., Grosbras and Paus 2002; Van Ettinger-Veenstra et al. 2009; Prime et al. 2010), we decided to perform a second experiment to compare the emerging perceptual changes between both stimulation protocols.

In this second experiment, we probed transsaccadic displacement detection with online single-pulse TMS (pulse duration, <1 ms) over the right FEF region. Here, we used a fixed stimulation intensity of 60% of maximum stimulator output (corresponding average intensity relative to individual MT, 110%). Three subjects reported unpleasant facial twitches (i.e., involuntary blinks of mainly the ipsilateral eye lid). The sensation vanished after a slight change of coil orientation in these subjects (with the coil now placed anterior to the handle with an approximate angle of 60–80° from sagittal axis). Before every experimental run, we confirmed correct coil positioning over the putative FEF region with the functional marker task as specified above. Within an experimental run, the subjects' heads remained rigidly stabilized and the coil held in position as described above. We focused on a detailed characterization of psychometric changes in transsaccadic perceptual integration and therefore restricted single-pulse TMS to one single point in time, shortly after saccade onset (median delay after saccade onset, 16 ms). The choice of this time-point was motivated by neurophysiological findings that describe a peak time of transthalamic CD influence on FEF activity at 24 ms after saccade onset (Sommer and Wurtz 2006). Transistor-transistor logic pulses controlled timing of TMS pulses.

Data Analysis

Eye movement data were low-pass filtered, visualized, and analyzed in Matlab by using the ILAB toolbox (Gitelman 2002) and self-written routines. Saccade onset and offset were determined by a fixed velocity criterion (threshold, 30° per second). Saccade start and end positions were determined as fixation periods preceding saccade onset and following saccade end, respectively. Cumulative gaussians were fitted to the perceptual response data in Matlab by using "psignifit," a toolbox that implements the maximum-likelihood method described by Wichmann and Hill (2001). Uncertainty of displacement reports and the point of subjective target stationarity (PSS) were described by slope and bias estimates of the fitted psychometric function, respectively. Since group values were not normally distributed for all conditions tested (as assessed by Shapiro–Wilk normality tests), group values are reported as median values (±median absolute deviation) and statistical analyses were performed with nonparametric tests (significance level, $P = 0.05$).

The goodness of fit of psychometric functions was evaluated by using deviance scores. Deviance D was calculated as the log-likelihood ratio between a fully saturated model with no residual error and the data model (Wichmann and Hill 2001). For all subjects and conditions, deviance scores (median D [±median absolute deviation], 4.76 [±1.89]) were found to be below their critical chi-square value.

Results

We probed the detection of transsaccadic displacements without and with prior cTBS over the right FEF region and with TMS over vertex as a control stimulation site. We will first demonstrate exemplary results of 2 sample subjects to illustrate the basic pattern of perceptual changes after right frontal stimulation in comparison to the nonstimulated control condition.

Exemplary Results

Figure 1*B* shows psychometric curves of 2 exemplary subjects for the blanking task. Without prior stimulation (Fig. 1*B*, black circles), both subjects were apparently able to detect transsaccadic displacements with high precision and accuracy: Slopes of corresponding psychometric curves (Fig. 1*B*, continuous lines) were steep, and the PSS was found near physical target nondisplacement in both subjects (subject MW, 0.79° [0.24°]; subject FO, 0.18° [0.37]° for leftward [rightward] saccades). These results agree with previous reports, showing that the transient blanking of a target stimulus efficiently counteracts SSD (Deubel et al. 1996; Ostendorf et al. 2010). Specifically, it has been shown that when a target stimulus is switched off during the saccade and only reintroduced 50–300 ms later, detection of transsaccadic target displacements sharply improves (Deubel et al. 1996). This effect is already apparent with temporal gaps as short as 50 ms and asymptotes at 200–300 ms intervals (Deubel et al. 1996), indicating that target absence directly after the eye movement might represent the crucial determinant of the blanking effect. Target blanking may indicate a possible violation of visual space constancy to the visuomotor system, favoring a reliance on internal eye position estimates (Deubel et al. 1996; Ostendorf et al. 2010). The high sensitivity for transsaccadic target displacements in the blanking task has commonly been taken as indication that reliable CD information is available in normal subjects and can be used efficiently in this task (Deubel et al. 1996).

When tested after cTBS over FEF (Fig. 1*B*, white circles), both subjects exhibited a systematic forward shift of the PSS for leftward saccades, one subject showed this perceptual bias for rightward saccades as well (Fig. 1*B*, dashed lines; subject MW, 1.44° [0.19°]; subject FO, 0.6° [0.69°] for leftward [rightward] saccades). The observed forward shift of the psychometric function was caused by a systematic tendency to report a backward jump when the target was actually stationary or even displaced in the forward direction. This perceptual bias implies that the eyes landed more forward than the subjects realized. But since saccade metrics did not change (see Table 1), the most likely explanation is that subjects experienced a hypometric internal representation of the saccade.

Fixation Task

In principle, a perceptual bias could also arise from impaired memory of the presaccadic target position. Single-pulse TMS over FEF may interfere with spatial short-term memory under static fixation conditions, at least for the maintenance of multiple objects (Prime et al. 2010). We addressed a possible interference with spatial memory by probing displacement detection in a fixation task. Figure 2*B* shows individual results in the fixation task for a condition without stimulation (black circles) and with prior cTBS over FEF (white circles). Psychometric functions (Fig. 2*B*, continuous and dashed lines, respectively) were slightly shifted in the backward direction for both saccade directions and conditions (average PSS, –0.4°), indicating that subjects exhibited a small tendency to report a forward jump when the target was actually stationary or even displaced in the backward direction. This forward bias under static fixation may reflect a foveal bias of spatial short-term memory (i.e., a systematic hypometricity of memory representations), consistent with previous psychophysical findings

Table 1

Oculomotor performance (group medians ± median absolute deviations)

	Leftward saccades			Rightward saccades		
	Control	FEF	Vertex	Control	FEF	Vertex
Amplitude error (degrees)	−0.54 ± 0.12	−0.51 ± 0.49	−0.46 ± 0.27	−0.57 ± 0.36	−0.42 ± 0.18	−0.74 ± 0.35
Amplitude scatter (degrees)	0.96 ± 0.14	0.75 ± 0.12	0.83 ± 0.12	0.70 ± 0.10	0.84 ± 0.16	0.63 ± 0.09
SRT (ms)	185 ± 9	176 ± 18	174 ± 16	182 ± 12	192 ± 20	178 ± 12
Peak velocity (degrees/s)	337 ± 36	335 ± 32	330 ± 21	361 ± 48	365 ± 46	343 ± 32

Note: Amplitude error was calculated as individual median horizontal amplitude error with negative values denoting saccade undershoots. Amplitude scatter was calculated as individual interquartile range of horizontal amplitude error. SRT and peak velocities were calculated as individual median values. No significant changes were observed between the nonstimulated control condition, the conditions with prior cTBS over FEF and with prior cTBS over vertex for any of these measures for leftward (Friedman ANOVA, $\chi^2 \leq 2.0$, $P \geq 0.40$) or rightward saccades (Friedman ANOVA, $\chi^2 \leq 2.67$, $P \geq 0.33$).

(Sheth and Shimojo 2001). However, psychometric functions in the nonstimulated control condition and the condition with prior cTBS completely overlapped and resulting detection thresholds were almost identical (average threshold, control condition, 0.43° [0.47°]; condition with FEF stimulation, 0.4° [0.5°] for leftward [rightward] saccades).

Supplementary Figure S2 shows PSS values in the blanking task (circles) and the fixation task (triangles) for the nonstimulated control condition (black symbols) and the condition with prior cTBS (white symbols). PSS values between the nonstimulated control condition and the condition with prior cTBS clearly differed for the blanking task with nonoverlapping 95% confidence intervals for leftward saccades in both subjects and for rightward saccades in one subject (FO) as well (with confidence intervals estimated by a bias-corrected accelerated [BCa] bootstrap method proposed by Wichmann and Hill (2001), based on 5000 runs). By contrast, PSS values in the fixation task were found to be virtually identical with overlapping confidence intervals.

Group Results

Similar to the exemplary results, a deterioration of displacement detection was observed for the whole group for leftward saccades following cTBS over the right FEF region (Fig. 3*A*). This perceptual impairment also manifested as forward shift of the PSS for leftward saccades (median PSS, 0.32° without prior stimulation, 1.12° with prior FEF stimulation). Significant differences between PSS values of the 3 tested conditions were confirmed for leftward saccades (Friedman analysis of variance [ANOVA], $\chi^2 = 12.7$, degrees of freedom [df] = 2, $P = 0.001$) and were caused by significantly different PSS estimates with prior FEF stimulation compared with the control condition (Wilcoxon signed-rank test, $P = 0.004$) and compared with prior vertex stimulation ($P = 0.04$), but no significant difference between control condition and vertex stimulation ($P > 0.05$). No significant difference between the 3 conditions was found for rightward saccades (Friedman ANOVA, $\chi^2 = 0.89$, df = 2, $P = 0.69$). Furthermore, no significant differences were observed between the slope values in the 3 conditions for leftward (Friedman ANOVA, $\chi^2 = 3.56$, df = 2, $P = 0.19$) or rightward saccades (Friedman ANOVA, $\chi^2 = 0.22$, df = 2, $P = 0.97$). The unchanged slope values argue against nonstationary perceptual performance (i.e., changes of perceptual detection thresholds with increasing time intervals after application of cTBS) that should inevitably affect the slope estimate of the psychometric function (Leek et al. 1991). For additional analysis of (non-)stationary perceptual performance, a running average of probe displacements generated by the 3 interleaved staircases was computed. This running average staircase level should give an estimate of the PSS dynamics over the course of the experiment. Average staircase levels approached a stable level within the first 30 trials and no systematic shift emerged over the remaining time course of the experiment (Fig. 4*A*). This analysis indicates that perceptual performance indeed remained stable over the course of the experiment.

For easier comparison between conditions, we determined a displacement threshold, that is, the absolute displacement necessary to obtain correct responses in 75% of trials for a given condition and subject (Ostendorf et al. 2010). Group results in the 3 resulting conditions (i.e., control condition

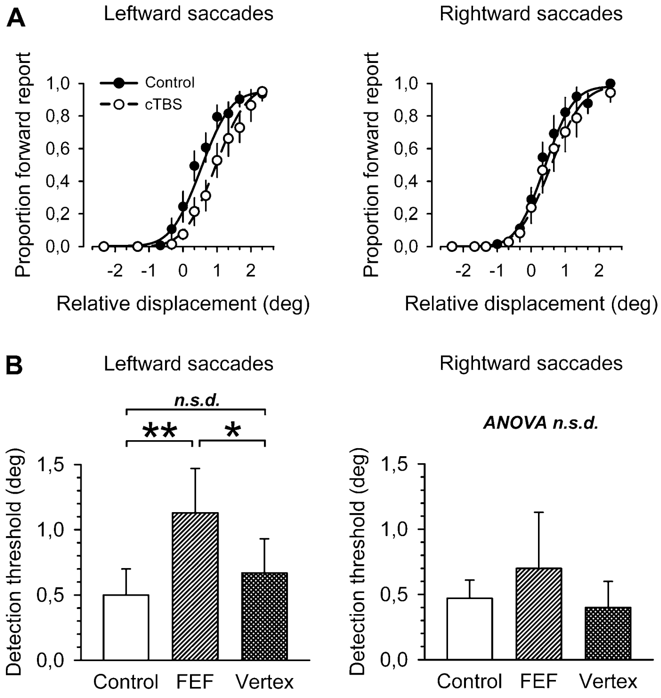

Figure 3. (*A*) Group average psychometric functions in the control condition without prior stimulation (Control, black circles and continuous lines) and in a condition with prior cTBS over FEF (cTBS, white circles and dashed lines). Error bars denote ±1 standard error of the mean of group average. Figure conventions otherwise follow Figure 1*B*. (*B*) Perceptual displacement thresholds, calculated as the absolute displacement needed to obtain 75% correct responses. Bars show median group thresholds (with error bars denoting median absolute deviation) for control condition and the conditions with prior theta-burst stimulation over FEF and vertex, respectively. Data are shown separately for leftward and rightward saccades. Asterisks (** and *) refer to significant pairwise differences (Wilcoxon test, $P = 0.004$ and $P = 0.027$, respectively); n.s.d., not significantly different.

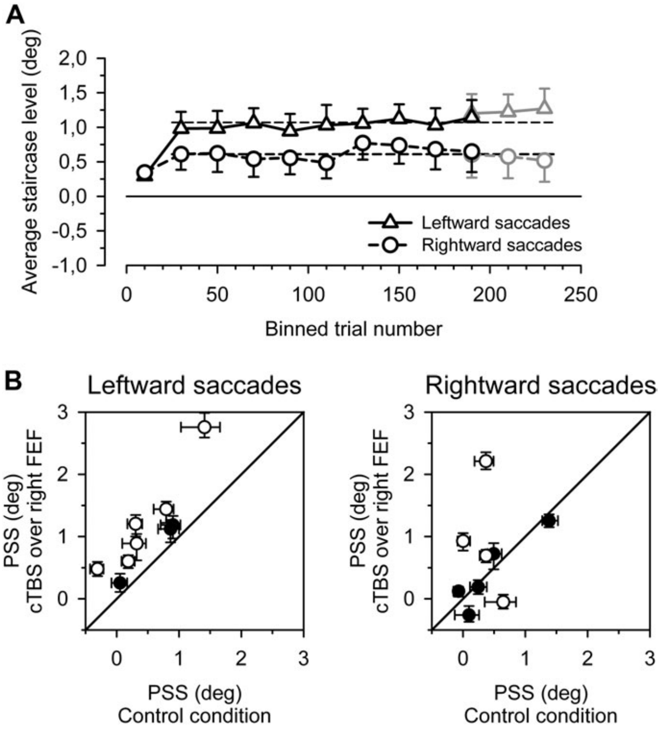

Figure 4. (*A*) Perceptual performance across test session with prior cTBS over the FEF region. We calculated the individual mean staircase level for consecutive trial triplets (i.e., trials with identical trial number within each of the 3 staircases) and averaged these values for bins of 20 consecutive trials. Figure shows running group averages, separately for leftward (diamonds and continuous black line) and rightward (circles and dashed black line) saccades, respectively. Error bars represent standard error. For the last 2 bins, data for only 8 subjects were available. To illustrate this matter, data of the 3 last bins are plotted separately for the remaining 8 subjects (gray symbols and lines). Dashed background lines denote the average displacement level for trial 20–240, with values corresponding closely to the PSS values obtained from the full psychometric function (average displacement level vs. PSS, 1.07° vs. 1.12° for leftward saccades and 0.61° vs. 0.69° for rightward saccades, respectively). (*B*) Individual PSS for the test condition with prior cTBS over the FEF region plotted against corresponding PSS estimates for the nonstimulated control condition. Data are shown separately for leftward and rightward saccades. Subjects with significantly different PSS estimates are shown as white circles (see main text for description of statistical analysis). Error bars denote the 95% confidence interval of the PSS as estimated by a BCa bootstrap method proposed by Wichmann and Hill (2001), based on 5000 runs.

without stimulation, test condition with stimulation over FEF, and with stimulation over vertex) are shown in Figure 3*B*. Without prior stimulation, median detection thresholds were 0.5° (0.47°) for leftward (rightward) saccades, respectively. These thresholds increased to 1.13° (0.7°) with FEF stimulation for leftward (rightward) saccades but remained similar to control condition after vertex stimulation (0.67° [0.4°] for leftward [rightward] saccades). Statistical analysis demonstrated significantly different thresholds for leftward saccades between these conditions (Friedman ANOVA, $\chi^2 = 12.7$, df = 2, $P = 0.001$). Post hoc tests on detection thresholds with leftward saccades confirmed a significantly different threshold for prior FEF stimulation compared with control condition (Wilcoxon signed-rank test, $P = 0.004$) and vertex stimulation ($P = 0.027$), but no significant difference between control condition and prior vertex stimulation ($P > 0.05$). For rightward saccades, no significant difference was found between the 3 conditions (Friedman ANOVA, $\chi^2 = 0.4$, df = 2, $P = 0.89$).

Lateralization of Behavioral Effect—Single-Subject Analysis

On a group level, significant changes of PSS estimates with prior FEF stimulation were observed for leftward saccades, that is, for saccades directed to the contralateral hemifield with respect to the stimulated FEF region. However, as can be appreciated from one of the sample subjects (subject FO in Fig. 1*B*), evidence for a bilateral effect was evident in some subjects. To further assess the degree of lateralization on a single-subject level, we statistically compared individual psychometric functions in the nonstimulated control condition with the corresponding FEF stimulation condition. We considered displacement detection to be significantly different when 2 criteria were met: First, we calculated confidence intervals for the PSS estimates as generated by a BCa bootstrap method proposed by Wichmann and Hill (2001), based on 5000 runs. We considered nonoverlapping 95% confidence intervals of PSS estimates as statistical indication for a significantly different PSS in both conditions. In addition, we compared the psychometric functions of the 2 conditions by using the Monte Carlo method implemented by pfcmp, a function from the psignifit toolbox (Wichmann and Hill 2001), based on 10 000 runs (significance level, $P = 0.05$).

We observed significantly higher PSS values in the critical test condition with prior cTBS over FEF compared with the control condition (with both criteria fulfilled, i.e., nonoverlapping confidence intervals and the additional statistical support for different underlying psychometric functions) in 6 (3) subjects for leftward (rightward) saccades, corresponding to 66.7% (33.3%) of all subjects tested. One subject showed a significantly lower PSS value for rightward saccades following cTBS over FEF compared with the control condition. Figure 4*B* plots corresponding individual PSS values for the condition with prior cTBS over the right FEF region versus the control condition.

Dependency on Saccade Amplitude

In our task, we probed the detection of transsaccadic target displacements for 2 target eccentricities, 8° and 10°. We employed different saccade amplitudes mainly to prevent subjects from performing preprogrammed and stereotyped eye movements. However, our design may allow for a further investigation of the observed systematic forward shift of the psychometric functions: If TMS-induced perceptual changes result from disturbed processing of saccade-related CD information, a dependency of the effect on corresponding saccade amplitudes might be predicted. We first confirmed significantly different amplitudes of saccades to the 2 target eccentricities (Wilcoxon signed-rank test, $P < 10^{-5}$ for both saccade directions; median amplitudes, 7.54° [9.51°] for leftward saccades, 7.52° [9.49°] for rightward saccades with target eccentricity of 8° [10°], respectively). In a next step, we analyzed individual performance separately for the 2 target eccentricities by fitting psychometric functions on the individually split data sets. Again, we observed a significant forward shift of the PSS for leftward saccades following cTBS over the right FEF region (Wilcoxon signed-rank test, $P = 0.004$ for both target eccentricities, see Fig. 5). Statistical analysis confirmed a significantly larger shift for trials with 10° target eccentricity compared with 8° target eccentricity ($P = 0.004$). No significant shift was observed for rightward saccades ($P \geqslant 0.25$). The scaling of the perceptual distortion with different

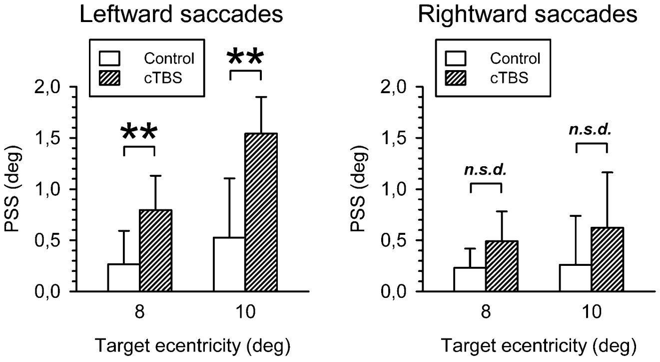

Figure 5. Dependency of the perceptual effect on saccade amplitude. Median estimates for the PSS of psychometric functions (with error bars denoting median absolute deviation). Data are analyzed separately for target eccentricities of 8° and 10°, respectively. PSS estimates are shown for the nonstimulated control condition (white bars) and the condition with prior cTBS over the FEF region (shaded bars), separately for leftward and rightward saccades, respectively. Asterisks denote significant different PSS estimates between control and test condition for leftward saccades (Wilcoxon signed-rank test, $P = 0.004$). Statistical analysis confirmed a significantly larger shift for trials with 10° target eccentricity compared with 8° target eccentricity ($P = 0.004$). No significant PSS difference was observed between control and test condition for rightward saccades and either target eccentricity ($P \geq 0.25$).

saccade amplitudes provides confirmative evidence for a putative disturbance of eye movement–related CD signals.

Oculomotor Performance

We ensured that the observed distortion of perceptual reports did not simply arise from changes in oculomotor performance. Single-pulse TMS (Müri et al. 1991; Thickbroom et al. 1996; Grosbras and Paus 2002) and cTBS (Nyffeler et al. 2006) over FEF has been shown to increase SRT for contraversive saccades, and we used this well-documented finding in our functional marker task for FEF localization. However, effects of frontal TMS on SRT have been shown to be restricted to endogenous nonreflexive saccadic eye movements (Müri et al. 1991; Thickbroom et al. 1996). The design of our blanking task with a sudden peripheral target onset together with central fixation offset arguably triggered a predominantly reflexive saccade mode (with a median SRT of 181 ms across subjects and conditions supporting this notion, see Table 1). Indeed, no significant changes in SRT were observed between the nonstimulated control condition, the conditions with prior cTBS over FEF and with prior cTBS over vertex for leftward (Friedman ANOVA, $\chi^2 = 1.65$, $P = 0.48$) or rightward saccades (Friedman ANOVA, $\chi^2 = 0.74$, $P = 0.74$).

To the best of our knowledge, no changes in saccade amplitudes or peak velocities have been documented so far with TMS over FEF (Nyffeler et al. 2006; Prime et al. 2010). In accordance with these null results in previous studies, no significant differences emerged in the present study for median amplitude error, saccade endpoint scatter, or saccadic peak velocity between the 3 conditions, neither for left- or rightward saccades (Friedman ANOVA, $\chi^2 \leqslant 2.67$, $P \geqslant 0.33$; see Table 1 for corresponding group values of individual conditions). In particular, systematic changes of saccade amplitudes induced by TMS might constitute a trivial reason for the observed systematic distortion of perceptual performance. We therefore conducted an additional analysis to check for a possible interindividual dependency of the systematic perceptual error (i.e., shift magnitude of the PSS) on systematic errors of saccade amplitudes (i.e., individual median amplitude error). However, neither for the critical test condition (i.e., leftward saccades with prior stimulation over FEF, Spearman–Rho correlation, $r^2 = 0.007$, $P = 0.83$) nor any other condition (Spearman–Rho correlation, $r^2 \leqslant 0.16$, $P \geqslant 0.28$) did a significant correlation between these measures emerge. Furthermore, no systematic changes of saccade amplitude error over the course of the experiment emerged for the critical test condition with prior stimulation over FEF (comparison of median saccade amplitude error between the first and last 25 percent of trials, Wilcoxon signed-rank test, $P = 0.2$ [$P = 0.82$] for leftward [rightward] saccades).

We also ensured that the metrics of secondary saccades, correcting for the artificially induced targeting error of primary saccades, were not influenced by frontal stimulation. Intercepts, slopes, and correlation coefficients (Spearman–Rho) of linear regressions between secondary saccade amplitudes and targeting errors of corresponding primary saccades yielded no significant differences between parameters in the control condition and the condition with prior theta-burst stimulation over FEF (pairwise statistical comparisons with Wilcoxon signed-rank test, $P = 0.074$ for comparison of correlation coefficient in rightward saccades, all other $P \geqslant 0.5$).

Neurophysiological studies demonstrated that transient pharmacological inactivation of the primate FEF may lead to systematic deviations of eye fixations in the direction ipsilateral to the inactivated FEF side (Sommer and Tehovnik 1997; Dias and Segraves 1999) and also in the downward direction (Sommer and Tehovnik 1997). We therefore performed an additional statistical analysis on presaccadic fixation positions. This analysis indicated no systematic changes for median fixation positions between the 3 conditions for left- or rightward saccades, neither in the horizontal (Friedman ANOVA, $\chi^2 \leqslant 1.56$, $P \geqslant 0.57$) nor vertical dimension (Friedman ANOVA, $\chi^2 \leqslant 0.24$, $P \geqslant 0.90$).

Displacement Detection with Online Single-Pulse TMS

Effects of single-pulse TMS on perceptual detection threshold were found to be similar compared with cTBS (see Fig. 6). Without stimulation, median detection thresholds were 0.42° (0.42°) for leftward (rightward) saccades. These thresholds increased to 0.93° (0.65°) with single-pulse FEF stimulation for leftward (rightward) saccades, reflecting a significant change of perceptual thresholds for leftward saccades (Wilcoxon signed-rank test, $P = 0.008$) but not rightward saccades (Wilcoxon signed-rank test, $P = 0.25$). Similar to the findings with prior cTBS, deterioration of displacement detection mainly arose from a forward shift of the PSS for leftward saccades (median PSS, 0.31° without stimulation, 0.91° with TMS over the right FEF region, Wilcoxon signed-rank test, $P = 0.008$). No significant change was noted for the PSS for rightward saccades ($P = 0.64$) or the slope values for either saccade direction ($P \geqslant 0.11$). We also ensured that saccade metrics did not change due to single-pulse TMS over the FEF region (see Supplementary Table S1 for corresponding group values). Indeed, no significant differences were observed for median amplitude error, saccade endpoint scatter, or saccadic peak velocity between the TMS condition and the control condition without stimulation, neither for leftward (Wilcoxon signed-rank test, $P \geqslant 0.25$) nor rightward saccades ($P \geqslant 0.11$).

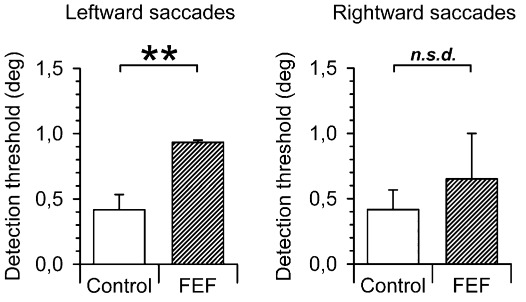

Figure 6. Perceptual displacement thresholds with online single-pulse TMS. Thresholds were calculated as the absolute displacement needed to obtain 75% correct responses. Bars show median group thresholds (with error bars denoting median absolute deviation) for control condition (no stimulation) and with online single-pulse TMS over FEF region. Data are shown separately for leftward and rightward saccades. Asterisks (**) refer to significant pairwise difference (Wilcoxon test, $P < 0.01$); n.s.d., not significantly different.

Discussion

In the present study, we used the detection of transsaccadic target displacements in a blanking task as a proxy to infer on the transsaccadic integration of visual space (Deubel et al. 1996). We observed that offline stimulation over the right FEF region impaired the transsaccadic integration of visual space for leftwards (i.e., contraversive) saccades. Specifically, subjects exhibited a systematic bias in the evaluation of transsaccadic target displacements. Additional analyses ruled out that the observed distortion of perceptual judgments was simply a side effect of oculomotor changes induced by TMS. A second experiment without intervening eye movements furthermore indicated that the observed bias in displacement detection did not arise from a disturbed internal representation of the presaccadic target position per se. We are thus left with the parsimonious explanation that subjects underestimated the amplitude of executed saccades: With an internal underestimation of executed saccade amplitudes, subjects will expect to land shorter of the target than they actually do. Subjects will thus on average predict a larger perceptual forward error after saccade execution than actually experienced, leading to the observed forward shift of the PSS.

Putative Mechanisms of TMS Interference Over Frontal Cortex

No changes of oculomotor performance were observed with prior cTBS or online single-pulse TMS over right frontal cortex. This finding is consistent with prior work, showing that TMS over FEF (Müri et al. 1991; Thickbroom et al. 1996; Ro et al. 1997, 1999; Nyffeler et al. 2006; Prime et al. 2010) or FEF lesions (Rivaud et al. 1994) did not alter metrics of reflexive saccades. Triggering of reflexive saccades may critically rely on different oculomotor areas like the posterior parietal cortex and superior colliculus (Pierrot-Deseilligny et al. 2002). However, the perceptual effect observed in our study suggests that the FEF is still involved in sensorimotor integration of visual space across this type of eye movements, presumably by the processing of reentrant CD information (Sommer and Wurtz 2006; Hamker et al. 2011).

Interestingly, the observed distortion of transsaccadic space integration is very similar to the perceptual impairment observed in a patient with a focal lesion within CD-transmitting portions of central thalamus (Ostendorf et al. 2010). Our findings furthermore bear resemblance to results obtained in a recent psychophysical study that also utilized a blanking task to probe perceptual space integration across saccades (Collins et al. 2009). In a critical condition of this study, subjects underwent saccade adaptation resulting in systematic amplitude changes before testing in the blanking task commenced. Perceptual judgments in this condition were systematically biased compared with a control condition with no prior saccade adaptation (Collins et al. 2009). This adds to our finding that CD information and corresponding eye movements may be dissociated by specific experimental manipulations, although in complementary ways: Results by Collins and coworkers would be consistent with an unaltered CD signal that did not include information about the systematic saccade changes induced by adaptation. On the other hand, biased perceptual judgments in the thalamic patient study (Ostendorf et al. 2010) and following FEF stimulation in our actual study may arise from altered internal monitoring information while corresponding saccade metrics remained unchanged.

As an alternative account for the perceptual changes observed in their study, Collins et al. (2009) invoked a restructuring of visual space induced by saccade adaptation. Following this account, the perceived location of a target before an eye movement might be altered by adaptation, while on the other hand, CD information would faithfully reflect adapted saccade metrics. This latter explanation receives support from findings on perceptual mislocalization effects that are induced by saccade adaptation regimes (Collins et al. 2007; Zimmermann and Lappe 2010) and that can be observed even under steady fixation (Zimmermann and Lappe 2010). A general alteration of visual space perception might in principle also serve as alternative interpretation for the perceptual effect induced by frontal stimulation in our study but would be difficult to reconcile with additional findings: Saccade amplitudes were not changed by FEF stimulation and perceptual changes in displacement detection were clearly related to intervening saccades since no perceptual changes were observed in the fixation task and the size of the perceptual effect scaled with saccade amplitude.

Recent electrophysiological findings assign a more comprehensive role to the FEF than just serving as relay station for CD input from subcortical structures: The reafferent postsaccadic response of a significant number of visual and visuomotor FEF neurons was shown to be tuned to the amount of intra-saccadic stimulus displacements (Crapse and Sommer 2008b). Therefore, frontal stimulation may not only involve interference with incoming CD information. Rather, stimulation over the FEF region may also disturb the consecutive integration of CD signals and presaccadic visual information for computation of an internal prediction of saccade-induced visual changes (Crapse and Sommer 2008c). Lastly, stimulation may interfere with processing of the mismatch encountered when comparing such an internal prediction with the actual visual reafference after saccade completion (Crapse and Sommer 2008b). These different levels of possible interference by TMS may, however, not be mutually exclusive and our behavioral findings cannot decide between them.

Perceptual Impairments Predominantly for Contraversive Saccades

The lateralized deficit in transsaccadic space integration is consistent with a predominant representation for contralateral visual space and contraversive saccade output within the primate FEF (Bruce and Goldberg 1985). It would also conform with the neurophysiological identification of lateralized CD pathways running from superior colliculus to the ipsilateral thalamus and FEF (Sommer and Wurtz 2006). However, recent neurophysiological findings indicate that transthalamic CD projections may not be strictly ipsilateral and that the FEF may receive information from both superior colliculi and hence the entire visual field (Crapse and Sommer 2009). Consistent with neurophysiological findings (Umeno and Goldberg 1997; Crapse and Sommer 2009), our results nevertheless suggest that the prevailing proportion of FEF neurons process CD of contraversive saccades. A representation of CD information for all saccade directions in each FEF (Crapse and Sommer 2009) or a predominance of the right human FEF for visuospatial processing (Grosbras and Paus 2002; Kagan et al. 2010) may explain why we observed a perceptual deficit for both saccade directions in 3 of our subjects.

Comparison between cTBS and Online Single-Pulse TMS

With both cTBS and single-pulse TMS over the right FEF region, we observed highly similar distortions of transsaccadic space integration. From a neurophysiological perspective, it is not obvious that both stimulation protocols should yield similar quantitative and qualitative changes in perceptual performance: Effects of cTBS are believed to arise from long-term depression-like changes in synaptic connectivity and consecutive alterations in cortical excitability (Stagg et al. 2009; Cárdenas-Morales et al. 2010). On the other hand, single-pulse TMS appears to briefly interfere with ongoing cortical processing by injecting a highly synchronized but random activity burst (Walsh and Cowey 2000). It is, however, not clear whether TMS effects might best be explained by a suppression of neural signals or the addition of random neural activity (Miniussi et al. 2010). Psychophysical findings indicate that online TMS may either disrupt processing of task-relevant information, leading to a reduction of signal strength (Harris et al. 2007), or alternatively add random activity, that is, noise, to ongoing processing in the stimulated cortical region (Ruzzoli et al. 2010). Apparently, in our study, both cTBS and single-pulse TMS protocols distorted the generation of internal prediction signals in a similar fashion: Stimulation systematically affected the PSS estimates, while the slopes of psychometric functions remained largely unaffected. In this context, effects of cTBS and single-pulse online TMS in our paradigm would be consistent with the suppression of task-relevant CD signal processing (Harris et al. 2007) rather than the injection of "neural noise" (Ruzzoli et al. 2010). It remains possible that different stimulation parameters (i.e., different simulation strength or time of stimulation) might lead to differential effects, especially for online single-pulse TMS.

Single-pulse TMS potentially offers additional information about the possible time-point of interference (Walsh and Cowey 2000). Interference by TMS at the chosen time-point in our study would be consistent with a disturbed processing of a transthalamic CD volley arriving at FEF (Sommer and Wurtz 2002, 2006). However, the onset of remapping activity for FEF neurons has been shown to vary considerably, spanning a broader perisaccadic time range (Sommer and Wurtz 2006). Indeed, a recent study observed maximum interference with transsaccadic memory for multiple objects by frontal TMS pulses applied within an extended time window before saccade onset (Prime et al. 2010). In this context, the successful interference by single-pulse TMS in the present study encourages a detailed investigation of the temporal dynamics in future studies with application of single-pulse TMS at different time-points with respect to saccade onset.

Comparison with Previous Studies

Applying nonfocal TMS over parietal but not over frontal regions has been shown to interfere with the perceptual integration of visual space (Chang and Ro 2007). However, the anatomical location of the frontal stimulation site in this study remains elusive with respect to the FEF region. Moreover, the specific perceptual detection task used in the present study may provide a more sensitive measure of updating capabilities (Ostendorf et al. 2010): The insertion of a brief temporal gap after saccade completion has been shown to effectively counteract saccadic suppression of displacement, presumably biasing visuospatial processing toward an efficient use of internal monitoring signals (Deubel et al. 1996).

The observed perceptual effect is consistent with an internal underestimation of leftward saccade amplitudes of about 11.5% with prior cTBS over the FEF region. Previous studies in non-human primates with transient inactivation of transthalamic CD pathways (Sommer and Wurtz 2002) and in patients suffering from focal thalamic lesions (Bellebaum et al. 2005; Ostendorf et al. 2010) used an oculomotor double-step task that requires CD for correct execution of a saccade sequence and reported an internal underestimation of saccade amplitudes of about 17–21%. In a recent study, in a thalamic stroke patient, we used a similar perceptual task as in the present study and observed an internal saccade underestimation of 11% (Ostendorf et al. 2010). Identical sign and similar strength of transsaccadic spatial updating impairments could point toward a common underlying disturbance, that is, a partial disruption of CD transmission. However, a comparison across different tasks and between patients with thalamic lesions, inactivation studies in non-human primates, and the effects of TMS over FEF may only allow for limited inferences. It however demonstrates a partial deficit in all cases, suggesting that other CD pathways may partially compensate for disturbances in distinct CD-processing thalamo-cortical nodes.

Our results conform to findings from a recent study on the role of the FEF in transsaccadic memory for multiple objects, suggesting that TMS over FEF interfered with spatial updating of object locations across saccades (Prime et al. 2010). Our present study provides direct evidence for a causal role of frontal activity in the transsaccadic updating of visual space with a task design that allowed for a psychometric characterization of emerging deficits. It furthermore complements previous work on the function of posterior parietal cortices in transsaccadic updating (Chang and Ro 2007; Morris et al. 2007; Prime et al. 2008). As a logical extension, it would be interesting to directly compare the spatial characteristics of updating deficits caused by interference with parietal and frontal activity.

Conclusions

Taken together, our results suggest that the integration of visual space across eye movements can be disturbed by interference with frontal activity. The pattern of impairment was found to be compatible with a compromised and incomplete remapping of visual space across saccades. These findings assign an important role to the human FEF in the matching of visual space across the frequent displacements induced by saccadic eye movements. It remains to be determined how our findings might translate to visual environments encountered in everyday life that typically provide additional visual reference information.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Funding

German Federal Ministry of Education and Research Grant (01GW0653) (Visuospatial-Cognition).

Notes

We are grateful to Felix Blankenburg and the Bernstein Center for Computational Neuroscience for generous technical support and the anonymous reviewers for very helpful comments on a previous version of this manuscript. *Conflict of Interest*: None declared.

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