Effect of TMS on Oculomotor Behavior but not Perceptual Stability during Smooth Pursuit Eye Movements

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During smooth pursuit eye movements, we do not mistake the shift of the retinal image induced by the visual background for motion of the world around us but instead perceive a stable world. The goal of this study was to search for the neuronal substrates providing perceptual stability. To this end, pursuit eye movements across a background stimulus and perceptual stability were measured in the absence and presence, respectively, of transcranial magnetic stimulation (TMS) applied to 6 different brain regions, that is, primary visual cortex (V1), area MT+/V5, left and right temporoparietal junctions (TPJs), medial parieto-occipital cortex (POC), and the lateral cerebellum (LC). Stimulation of MT+/V5 and the cerebellum induced significant decreases in pursuit gain independent of background presentation, whereas stimulation of TPJ impaired the suppression of the optokinetic reflex induced by background stimulation. In contrast to changes in pursuit, only nonsignificant modifications in perceptual stability were observed. We conclude that MT+/V5, TPJ, and the LC contribute to pursuit eye movements and that TPJ supports the suppression of optokinesis. The lack of significant influences of TMS on perception suggests that motion perception invariance is not based on a localized but rather a highly distributed network featuring parallel processing.

Keywords: Flehne illusion, optokinetic reflex, perceptual stability, smooth pursuit eye movements, transcranial magnetic stimulation, visual motion perception

Introduction

To maintain a sense of perceptual spatial stability despite self-motion is an important requirement for successful spatial orientation (Sommer and Wurtz 2008). For this, the brain has to discriminate sensory signals due to the observer’s own activities from others that arise from changes in the external world. Eye movements such as smooth pursuit eye movements may serve as a case in point. They allow us to stabilize the image of a selected object on or close to the fovea in order to make use of the advantages offered by foveal vision (Haarmeier and Thier 1999, 2006). The inevitable consequence, however, is that the images of all other objects (the “visual background”) will, if stationary in the world, move on the retina at a speed corresponding to the eye rotation carried out. This kind of eye movement induced retinal image motion must not be mistaken for movement of the world around us. Otherwise, our concept of a stable world would be lost (Haarmeier et al. 1997).

Building on early suggestions by von Helmholtz (1867) and supported by extensive psychophysical work (e.g., Wertheim 1994; Banks et al. 1996; Haarmeier et al. 2001), the inferential theory of perception holds that our ability to distinguish between external stimuli and self-induced sensory stimuli is achieved by subtracting an internal reference signal (RS), termed the “Willensanstrengung” (the effort of will) by von Helmholtz (1867) and the “Efferenzkopie” (the efference copy) by von Holst and Mittelstaedt (1950), from the sensory signal. Specifically, perceptual stability in the case of smooth pursuit eye movements is thought to be accomplished by subtracting a copy of the eye movement motor command from the retinal motion signal (Wertheim 1994). If the 2 cancel each other, visual structures, which do not move, will be perceived as nonmoving. However, efference copy information alone seems insufficient in order to guarantee perceptual stability (Bridgeman 2007) due to instance to neuronal delays or dependencies of visual motion signals unrelated to eye movements. Therefore, a current concept of the RS is an optimized description of the expected visual consequences of the eye movement (Haarmeier et al. 2001), which is derived from and supplemented by different sources, including not only efference copy information on the motor command but also sensory signals such as vestibular or visual components.

Although the perception of visual motion during pursuit eye movements has been the subject of many psychophysical studies (e.g., Flehne 1922; Mack and Herman 1973; Wertheim 1994; Haarmeier and Thier 1996; Freeman 1999; Freeman et al. 2000; Haarmeier et al. 2001) that have carefully described its dependencies on various visual and oculomotor parameters, comparably few studies have been performed so far addressing its neuronal underpinnings. Some human studies using functional brain imaging techniques searched for neuronal responses that would correlate with motion perception during pursuit eye movements rather than the physical attributes of the visual stimulation (visual evoked potentials: Haarmeier and Thier 1998, functional magnetic resonance imaging [fMRI]: Lindner et al. 2006; Trenner et al. 2008, magnetoencephalography [MEG]: Tikhonov et al. 2004). Consistently, these studies have found that early components of the visual responses elicited by pursuit across a stationary visual stimulus, that is, responses attributed to area V1 up to area hMT+/V5, did not reflect motion perception but the retinal motion signal prevailing. This finding is in good agreement with single cell recordings in rhesus monkeys showing that the fraction of real-motion cells, that is, cells that respond to motion in world/head-centered coordinates, rather than pursuit-induced retinal image motion is small in early visual cortex but increases along the cortical hierarchy of visual motion processing with a significant fraction of real-motion cells present, for example, in area V3A (Galletti et al. 1990) or area MST (Erickson and Thier 1991, see Galletti and Fattori 2003 for review).

In contrast to early visual cortex, activity of comparably late visual areas has been found to correlate with motion...
perception during pursuit eye movements. A first region described by Tikhonov et al. (2004) using MEG was located in the dorsomedial aspect of parieto-occipital cortex (POC), a region also activated during stationary fixation by large optic flow stimuli (Previc et al. 2000; Dukelow et al. 2001). The possibility that this area might play a specific role in the processing of large visual motion stimuli has further been suggested from the demonstration of posintron emission tomography activations correlated with the perception of circular vection (Brandt et al. 1998). Recent imaging studies (Pitzalis et al. 2006, 2009; von Pfostl et al. 2009) suggest that the medial POC houses the human homologue of monkey area V6 (Galletti et al. 1999, 2003) for which a fundamental role in the representation of visual motion has been established. Importantly, most of the neurons in V6 are of the real-motion type (Galletti and Fattori 2003) and are thus a highly plausible candidate for perceptual invariance during pursuit (for a recent review of area V6 in the human and macaque brain, see Fattori et al. 2009). A second visual area that showed blood oxygen level–dependent (BOLD) responses reflecting the percept of visual background motion during pursuit eye movements was the parieto-insular cortex (Lindner et al. 2006, fMRI) and retinoinsular cortex at the temporoparietal junction (TPJ, Trenner et al. 2008, fMRI), assumedly congruent with the putative human homologues of the parieto-insular vestibular cortex (PIVC) and the visual posterior sylvian area (VPS), respectively, characterized in the monkey brain (Gürsser et al. 1990a, 1990b; Guldin and Gürsser 1998; Dicke et al. 2008). Interestingly, the cortex in the posterior part of the insula showed responses also correlating with the percept of vection in the study by Brandt et al. (1998).

Somewhat surprisingly, BOLD responses outside the cerebral cortex have also been found to change in concert with the percept of motion. Specifically, Lindner et al. (2006) showed that responses in the lateral hemispheres of the cerebellum emphasizing CRUS I were modulated in accordance with motion perception during pursuit. Likewise—albeit localized in the nodulus—cerebellar BOLD responses were more active during perceived self-motion in a human MRI study on circular vection (Kleinschmidt et al. 2002). Based on the inferential theory of perception and in view of the important role of the cerebellum in motor control, the unexpected finding of percept-related cerebellar activity could reflect efference copy information.

Notably, 2 of the areas that have been described so far to change activity along with motion perception during pursuit eye movements, that is, parieto-insular cortex and cerebellum, lie outside the classical dorsal stream of motion processing, and their suggested role in motion perception has been inferred only indirectly from imaging studies based on correlation analysis. A first goal of the present study, therefore, was to test the contribution of these areas to perceptual invariance during pursuit by means of transcranial magnetic stimulation (TMS). Besides perception, also pursuit performance was measured and analyzed for the different conditions of stimulation. This combination allowed us to demonstrate that stimulation of the area MT+/V5 (in the following referred to as MT+), the lateral cerebellum (LC), and the parieto-insular cortex impairs pursuit behavior but leaves the percept of visual motion unchanged. This dissociation suggests a widely distributed and parallel network elaborating motion perception, whereas pursuit performance is controlled by a more distinct network emphasizing serial processing.

Materials and Methods
Subjects
Twelve healthy subjects, 4 males, including one of the investigators (TK), and 8 females, participated in the experiments (age: 22–41 years). All of them had normal or corrected-to-normal visual acuity. Subjects gave their written informed consent according to the declaration of Helsinki and the guidelines of the local Ethics Committee of the Faculty of Medicine of the University of Tübingen, which approved the study.

Visual Stimulation and Psychophysical Procedure
Subjects executed linear rightward smooth pursuit eye movements across a background stimulus, a random dot pattern of low contrast briefly presented while the eyes were close to straight ahead (Fig. 1). Stimuli were rear projected onto a large translucent screen (frame rate 72 Hz, 1280 × 1024 pixels) positioned at a viewing distance of 145 cm in a dark experimental room. Viewing was binocular. A red dot (diameter 10 min of arc) served as the pursuit target, which was presented for 0.5 s in the middle of the screen at the beginning of each trial. The target next jumped 15 deg to the left and then moved to the right at a constant velocity of 12 deg/s spanning a visual angle of 30 deg. Temporally located in the middle of the target sweep, the background pattern was presented for 300 ms. Short presentation times were chosen in order to induce the erroneous percept of background motion (see below). The background stimulus subtended 42 × 38 deg of visual angle and consisted of 250 white dots (diameter 15 min of arc, luminance 3.6 cd/m² as compared with the otherwise dark background). Subjects were required to track the pursuit target as accurately as possible and to indicate at the end of each trial whether they had seen the background moving to the right or to the left (2-alternative forced choice).

In order to exactly quantify the background motion perceived, we determined the velocity of external horizontal background motion required to yield the percept of a stationary background (Mack and Herman 1973). To this end, the velocity of coherent horizontal background motion was varied by an adaptive staircase procedure (Lieberman and Pentland 1982), converging on a point of subjective stationarity (PSS). At the PSS, the velocity of external horizontal background motion necessary to render the background perceptually stationary provides 2 pieces of information. First, the background velocity at PSS is equal in magnitude but opposite in direction to the motion (erroneously) perceived during pursuit across a physically stationary stimulus, that is, it serves as an operational measure of the so-called Filehne illusion (Filehne 1922). Second, at the PSS, the physical background velocity cancels the component of pursuit-induced retinal image motion, which has not been compensated for by the RS. Accordingly, a background velocity at PSS (V_p) of 0 deg/s reflects an ideal RS able to fully compensate for pursuit-induced image motion. In contrast, a PSS corresponding to the velocity of the eyes indicates a complete lack of this signal. Following the suggestion of Lindner et al. (2006), we will therefore use a “reference signal gain” index (RS gain) to characterize the size of the RS. It is given by

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\text{RS gain} = \frac{V_p - V_{PSS}}{V_p}
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Each single experiment included 55 trials that were initiated by the subject by means of a button press. The background velocity presented in the first trial was set 4 deg/s (to the right) and following trials were controlled by the staircase procedure. The first main perceptual measure, that is, the PSS was defined as the background stimulus velocity that resulted in 50% right and 50% left responses. It was determined by means of a probit analysis (McKee et al. 1985) with subsequent chi-square goodness-of-fit tests. Based on this approximation also, the slope of the function relating subjectively perceived motion to physical motion was determined given by the difference in background velocities observed for 25% and 75% right-hand responses. The 3 psychophysical measures, that is, background velocity at PSS, RS gain, and steepness of the psychometric functions were determined in all 12 subjects in the absence and presence of TMS as described below.
**Recording of Eye Movements**

Subjects were instructed to track the pursuit target as accurately as possible while avoiding head movements the latter supported by a chin rest. During all experiments, eye movements were monitored using a custom-made video system taking the pupil’s center as measure of eye position. Recordings were stored at a sampling rate of 50 Hz on an SGI workstation synchronized with a second workstation, which generated the visual stimuli. The records were low-pass filtered with a cut-off frequency of 15.9 Hz and analyzed offline on a single trial basis. Horizontal eye position traces were differentiated to obtain velocity and acceleration profiles. Saccades were detected based on acceleration criteria and also controlled by visual inspection. In most cases, the threshold for saccade detection was set 150 deg/s². If necessary, this threshold was adjusted and increased up to 250 deg/s² in order to avoid false positive detections. After elimination of saccades, the velocity profiles were averaged for each individual measurement across trials resulting in one mean horizontal velocity profile per measurement that finally was subjected to statistical group analysis.

**TMS**

Subjects were stimulated with a Medtronic Magpro stimulator (Skovlunde, Denmark, green box) in the biphasic mode, using a figure-of-8 coil, MC-B70. We used an event-related approach in which magnetic pulses were applied during presentation of the background stimulus. Stimulation was performed at 10 Hz and started with background stimulus onset thus resulting in 3 single pulses (Fig. 1). Single-pulse duration was 340 µs. Stimulation intensity was set to 50% of maximum output intensity in 7 subjects. In the remaining 5 subjects, a stimulation test revealed side effects at 50% (stimulation of the facial and trigeminal nerve). In these subjects, we reduced intensity to 50% of maximum output intensity in 7 subjects. In the remaining 5 subjects, a stimulation test revealed side effects at 50% (stimulation of the facial and trigeminal nerve). In these subjects, we reduced intensity to a just tolerable level, ranging from 40% to 46%. Mean motor threshold determined for the abductor pollicis brevis muscle of the right hand was 34.9% of the maximum stimulator output.

Prior to the psychophysical experiment, coil position in relation to the head was determined and registered in all 3 translational degrees of freedom (dfs) in a separate session using the frameless stereotactic positioning system BrainSight (V. 1.7, Rogue Research Inc, Montreal, Canada). Brain anatomy of the individual subjects was measured on a Siemens Sonata 1.5-T MR scanner (TR = 1.3 s, TE = 3.22 ms, TI = 660 ms, flip angle = 15 deg. 192 sagittal slices, matrix 256 x 256, and voxel size = 1 x 1 x 1 mm). The location of the stimulation sites was determined a priori on the basis of anatomical landmarks for area MT+, the TPJ, medial POC, and LC (Fig. 2) or on the basis of both anatomical and functional criteria (area V1). As shown by many studies, human area MT+ can be localized reliably in the ascending limb of the posterior part of the inferior temporal sulcus (Watson et al. 1993; Tootell et al. 1995; Wilms et al. 2005). Because area MT+ is believed to house both areas MT and MST (Becker et al. 2008) with the latter contributing to ipsiversive pursuit (Dukelow et al. 2001) and because our experiments involved pursuit eye movements always directed to the right, we decided to confine the stimulation of area MT+ to the right cerebral hemisphere. A second stimulation site was chosen in medial POC as marked by the border between the parietal lobe and the cuneus of the occipital lobe. Stimulation was applied 1-2 cm right from midline because a recent MEG study had revealed percept-related activity in the POC with a right-hemisphere dominance (Tikhonov et al. 2004). The TPJ was identified at the posterior end of the Sylvian fissure. In the case of TPJ, we decided to stimulate both hemispheres because on the one hand fMRI experiments had pointed toward the left TPJ to correlate with motion perception during pursuit (Lindner et al. 2006) and on the other hand pursuit contributions of cortical areas generally tend to exhibit ipsiversive preferences (e.g., Heide et al. 1996). Stimulation of the cerebellum was targeted at the most lateral extension of its right hemisphere. Finally, the primary visual cortex (V1) was identified by eliciting phosphens from the midline occipital pole following well-established routines (Kammer et al. 2005). The different stimulation sites were marked on a nonrelocatable swimming cap using BrainSight and then revisited during behavioral testing according to the following protocol.

Figure 1. Sketch of the stimulus (A) and course of an exemplary trial (B). The subject performed smooth pursuit eye movements (gray curve in B) by tracking a small dot that moved at 12 deg/s to the right (black curve in B). When the eyes were close to straight ahead a random dot pattern, the “background” was presented for 300 ms (gray column in B). The subject was instructed to maintain pursuit and to report the direction of perceived background motion by pressing 1 of 2 alternative keys. During background presentation, 3 pulses of TMS were applied at 10 Hz, indicated by arrows.

Figure 2. Synopsis on the different brain areas stimulated by TMS. The locations of right MT+, left TPJ, medial POC, and the right LC are shown for an exemplary subject. Sagittal, coronal, and axial section images are supplemented by 3D reconstructions of cerebral cortex as obtained from BrainSight. The remaining stimulation sites visual cortex V1 and right TPJ are not shown. R, right and L, left.
Each subject started his series with 3 control measurements performed without TMS. These initial runs were followed by a first pair of measurements during which TMS was applied to one of the 6 target sites. After a further control measurement, a second pair of TMS measurements would follow, this time with magnetic stimuli applied to a different region. The whole sequence was finished after all 6 stimulation sites had been visited and a final control had been performed. In total, thus each subject participated in 9 (= 3 × 1 + 1 + 1 + 1 + 1) control and 12 (= 6 [sites] × 2 [repetitions]) TMS measurements. The sequence of stimulation sites was randomized for each subject.

For group analysis, we averaged the behavioral responses in each subject across time bins of 80 ms for the 7 different conditions (1 control, 6 × TMS), separately. Averaged data of smooth pursuit velocity and behavioral responses were subjected to repeated-measures analysis of variance (ANOVA, Statistica V8.0, StatSoft, Tulsa, OK). The Huynh-Feldt (H-F) procedure was applied to correct degrees of freedom (Huynh and Feldt 1976). The H-F correction was used whenever a significant violation of the sphericity assumption was detected in repeated-measures ANOVA (with more than 2 df, see Vasey and Thayer 1987). The corrected degrees of freedom as well as epsilon are reported.

**Results**

**Influences of TMS on Pursuit Performance**

In all conditions, including the control measurements, presentation of the large random dot pattern, the visual background, resulted in transient decreases in pursuit velocity (Fig. 3). This was expected because structured visual backgrounds like the one used in the present study tend to impair smooth pursuit eye movements (Yee et al. 1983; Keller and Khan 1986; Kimmig et al. 1992; Mohrmann and Thier 1995; Haarmeier and Thier 1996). Such influences are considered manifestations of the optokinetic reflex (OKR), which is automatically initiated whenever large images move coherently on the retina. During pursuit, the OKR is triggered by the self-induced retinal image motion and is directed opposite to the pursuit movement. Therefore, in order to maintain pursuit, the OKR has to be suppressed. As shown in Figure 3, which plots the velocity profiles for all the different conditions, there was clear evidence for both the initiation and also the following suppression of the OKR. Pursuit velocity before background presentation was close to 12 deg/s under all conditions, that is, close to target velocity and then started to markedly decrease around 110 ms after background stimulus onset. After passing a nadir at around 220 ms, pursuit velocities increased again, however, without completely regaining initial values.

Although this principle pattern of pursuit eye movements was observed in all conditions, TMS as compared with the control condition induced significant deviations. Two types of changes resulting from TMS were apparent (Figs. 3 and 4). The first effect observed for stimulation of area MT+ and the LC (Figs. 3 and 4) was a general reduction in pursuit gain, which seemed more or less independent of the time course of changes induced by OKR but rather resulted in a downward shift of the whole pursuit trace. A second kind of effect, qualitatively different from this first one, resulted from stimulation of the TPJ (TPJ_l, TPJ_r) (Figs. 3 and 4). Here, pursuit traces for the conditions of TMS and controls were largely overlapping and in fact indistinguishable up to the final third of background presentation. Thereafter, however, the recordings were clearly diverging. Although under the control condition pursuit velocities were restored against the forces of OKR, suppression of the OKR was much more incomplete after TMS of the TPJ resulting in a larger and more enduring dip in the pursuit profile. Different to the stimulation sites addressed so far, TMS had only small (V1) or negligible (POC) influences on pursuit for the other sites.

In order to statistically test for the influences of TMS on pursuit performance and also their time courses and relation to OKR, we averaged pursuit velocities across temporal bins of 80 ms each (Fig. 4) and subjected the data to a repeated-measures ANOVA with the factors TIME (4 windows: 0–80, 100–180, 200–280, and 300–380 ms after background onset) and REGION (7 levels, control condition and 6 TMS conditions). This analysis revealed a significant main effect for the factor TIME ($F_{(16, 66)} = 18.0, P = 0.0002, \epsilon = 0.49$) and a significant interaction for TIME × REGION ($F_{(28, 855)} = 2.41, P = 0.022, \epsilon = 0.43$), whereas the factor REGION did not reach significance ($F_{(6, 66)} = 1.15, P = 0.34$). The main effect for TIME indicated that pursuit velocity significantly decreased during background presentation reaching the lowest values of 8.5 ± 0.42 (mean ± SEM) within 200–280 ms. In other words, under all conditions OKR induced a highly significant decrease in pursuit velocity.

In order to investigate the influence of TMS on the different regions, we broke down the interaction TIME × REGION applying 2-factor repeated-measures ANOVAs for each TMS region with the factors TIME (4 windows) and CONDITION (2 levels: control and the given TMS region). Significant CONDITION effects, that is, decreases in overall pursuit velocity resulting from TMS, were found for the stimulation of MT+ ($F_{(1,11)} = 7.80, P = 0.017$), the right TPJ ($F_{(1,11)} = 10.6,$...
P = 0.0077), and the LC (F(1,11) = 5.48, P = 0.039) while being nonsignificant for the other sites. Finally, statistically significant interactions between TIME and CONDITION were found for the TPJ of both hemispheres (TPJ_r: F(1.95, 21.5) = 4.48, P = 0.024, ε = 0.65; TPJ_l: F(1.43, 15.7) = 5.56, P = 0.022, ε = 0.48). These interactions reflected the fact that decreases in pursuit velocity resulting from TMS of the TPJ were not invariant for the 4 different time periods as indeed obvious from Figures 3 and 4.

It is important to note that the background stimulus velocity presented in a given measurement was not set a priori but followed an adaptive staircase procedure in order to determine the psychophysical thresholds of interest. As a consequence, the background velocities presented during control and TMS sessions were not exactly the same. As will be presented in the following section in detail, these differences were very small and indeed inappropriate to account for the differences in pursuit performance. Specifically, the differences between mean background velocity of the control measurements and the corresponding TMS experiments were as follows: V1, 0.08 deg/s, P = 0.7, t-test; MT+, 0.005 deg/s, P = 0.66; POC, 0.60 deg/s, P < 0.001; TPJ_r, 0.21 deg/s, P = 0.054; TPJ_l, 0.20 deg/s, P = 0.08; LC, -0.13 deg/s, P = 0.15). In other words, the only significant difference was observed for stimulation of POC, that is, the area for which no change in pursuit was observed. In other TMS conditions with marginal differences such as observed for TMS of areas TPJ_r and TPJ_l, the difference in background velocity as compared with the control was positive (0.21 and 0.20 deg/s, respectively) denoting that the background was moving on average somewhat faster to the right. Because this was the same direction as pursuit, this difference would, if anything, have supported rather than compromised pursuit eye movements during TMS as compared with control.

Influences of TMS on Background Motion Perception
Corroborating earlier findings obtained for short background presentation times (Haarmeier et al. 2001), the visual configuration employed in this study was associated with a classical Filehne illusion of around 25% (Filehne 1922), that is, subjects tracking a target that moved at 12 deg/s to the right experienced erroneous background motion to the left in the order of 2--3 deg/s (Fig. 5A). This was indicated by the fact that in the absence of TMS and for the group of subjects the mean velocity at PSS was 2.35 deg/s (to the right). Based on the actual eye movements carried out under the control condition, this PSS value denoted a RS gain of 0.75 (Fig. 5B). As evident from Figure 5, all TMS conditions resulted in similar measures with the highest RS gain observed after stimulation of LC (0.74) and the lowest observed after stimulation of POC (0.68). Thus, all

Figure 4. Influences of TMS on pursuit velocity. Means and standard errors (SEM, 12 subjects) of the difference in pursuit velocity between the control condition and the various TMS conditions, plotted for time windows of 80 ms each. Background stimulus presentation starts at 0 ms.
RS gains observed during TMS were lower than the control RS of 0.75; however, none of them was statistically significantly different (ANOVA with the factor REGION, $F_{(6,66)} = 1.4$, $P = 0.23$). Likewise, the slope of the function relating subjective perceived background motion to objective physical background motion, given by the difference between background velocities resulting in 25% and 75% right-hand responses (Fig. 5C), was not depending on TMS (ANOVA with the factor REGION, $F_{(6,66)} = 0.46$, $P = 0.83$).

The only stimulation site that suggested some influence of TMS on motion perception was POC. Based on the control condition, the mean RS here was reduced by 7%, however without reaching statistical significance. In order to explore whether TMS of POC might be effective with higher stimulation intensities, we added a new series of measurements to 4 of our subjects who had tolerated stimulation intensities of 50% without any difficulty. This series again included preceding ($n = 2$) and intermingling ($n = 2 \times 1$) controls flanking 2 pairs of TMS conditions, both with TMS applied to POC, 1 at 60% and the other at 70% the maximum output intensity. Figure 6 shows the result of the TMS measurements applied to POC. As can be seen for the individual subjects and the 3 stimulation intensities, differences between the RS gain under conditions of TMS as compared with the control were overall small, in fact smaller than intersubject variability. Furthermore, there was no evidence for stronger effects with higher intensities, and finally, even for a planned comparison based on paired $t$-statistics including all data ($n = 20$) the difference in RS gain between the 2 conditions did not reach the level of statistical significance ($P = 0.11$).

**Discussion**

Smooth pursuit eye movements induce retinal image motion, thus causing a problem for the brain: The self-induced sensations must be discriminated from the retinal inputs that represent physical motion in our environment. It has been suggested that the neuronal circuits solving this problem in the primate brain resort to efference copy information (Sperry 1950; von Holst and Mittelstaedt 1950; Wertheim 1994), which is calibrated on the basis of previous experience (Haarmeier et al. 2001) in order to provide a precise description of upcoming sensations. According to the inferential theory of perception (Sperry 1950; von Holst and Mittelstaedt 1950; Wertheim 1994), spatial stability despite pursuit eye movements is achieved by comparing the sensory signals reflecting retinal image motion with appropriate RSs derived primarily from internal sources. The present TMS study was performed in order to identify elements of the circuits essential for perceptual stability, that is, those parts of the brain housing the visual signal, the nonretinal RS, or the comparator of the 2. Stimulation sites were defined according to previous functional imaging studies on humans showing that activity observed in the TPJ, POC, and also the cerebellum correlated with motion perception during pursuit eye movements (Tikhonov et al. 2004; Lindner et al. 2006; Trenner et al. 2008). These areas have also been implicated in the perception ofvection (Brandt et al. 1998; Kleinschmidt et al. 2002). TMS of these candidate regions was supplemented by stimulation of
influence of TMS on Smooth Pursuit Eye Movements

Smooth pursuit eye movements are controlled by a network of cortical and subcortical brain regions that include visual cortex such as area V1 and MT/MST, the frontal and supplementary eye fields, thalamus, the pontine nuclei, and parts of the cerebellum, in particular the flocculus/paraflocculus and the posterior vermis (for review see Ilg and Thier 2005). Although smooth pursuit eye movements and their neuronal basis have been thoroughly characterized in animal models and human studies, the interactions between pursuit eye movements and optokinetic visual stimuli have been studied only sparsely so far. Recent studies have demonstrated influences of TMS on pursuit eye movements when applied to parietal (Hutton and Weekes 2007) or frontal cortex (Gagnon et al. 2006; Drew and van Donkelaar 2007; Nuding et al. 2009). To our knowledge, the present study is the first one using TMS to address interactions between pursuit and optokinetic stimuli and to test pursuit performance for the specific brain regions chosen here.

TMS induced significant effects at most stimulation sites. Two different types of effects were observed. A first one, found after stimulation of area MT+ and the LC, was a reduction in pursuit gain independent of influences of background presentation. This observation is totally in line with the reduction in pursuit gain observed in the monkey model after lesions of the MT--MST complex (Newsome and Wurtz 1988) and likely reflects contributions to the maintenance of ipsiversive pursuit offered by visual tracking neurons that are found in a subregion of area MST, the so-called area MSTI (Thier and Erickson 1992). A similar effect was observed after stimulation of the LC, a deficit that has not been described so far in human studies. This deficit resembles the pursuit impairment recently reported after surgical removal of the lateral cerebellar lobules H-VII in the rhesus monkey (Ohki et al. 2009). The precise functional role of this part of the cerebellum to oculomotor control has not yet been defined. Functional imaging studies in humans have observed stronger activations in this area under oculomotor conditions that impose attentional or working memory demands (Dieterich et al. 2000; Nitschke et al. 2004) suggesting cognitive contributions. As addressed already in the Introduction, Lindner et al. (2006) reported that BOLD responses in the lateral cerebellar hemispheres correlated with the percept of motion during pursuit pointing to the possibility that efference copy information might be present and, based on the known role of the cerebellum in adaptation, possibly also shaped in that region. Perceptual modifications were not part of the present experimental paradigm, thus leaving the possibility of false negative results with respect to perception. In any case, the similarity between deficits observed after stimulation of the MT+ complex and the LC suggests a functional interplay between these 2 regions that might not necessarily be confined to pursuit eye movements.

A second type of pursuit impairment resulting from TMS was observed in TPJ of both hemispheres. This deficit developed during the period of background presentation and in fact was most pronounced at the end of background stimulation, that is, at the time of OKR suppression. The change in pursuit induced by TMS of the TPJ cannot directly be inferred from previous studies because a role of the TPJ in pursuit has not yet been established. The hallmark of the TMS effect was a delayed and incomplete resaturation of pursuit velocity against the forces of OKR suggesting that the TPJ might contribute to the suppression of optokinetic influences. We chose the anatomically descriptive label of TPJ to avoid implying a single visual area. In fact, the homologies between human areas located in and posterior to the sylvian fissure and the corresponding macaque areas are a matter of debate. As recently supported by cytoarchitectonic mapping (Eickhoff et al. 2006), most human fMRI studies have ascribed BOLD responses at the TPJ to the human homologues of areas PIVC and VPS, originally described in the squirrel monkey and regarded as 2 of the core elements of the vestibular cortex (Grüsser et al. 1990a, 1990b; Gulden and Grüsser 1998). In agreement with this assignment, activations of the posterior parietal operculum/the posterior insular, that is, the suggested homologue of area PIVC, and activations encroaching onto the retroinsular cortex, that is, the presumed homologue of area VPS, have been described in functional neuroimaging studies using caloric (Bottini et al. 1994, 2001; Deutschländer et al. 2002; Fasold et al. 2002; Naito et al. 2003) and galvanic vestibular stimulation (Lobel et al. 1998, 1999; Bense et al. 2001; Fink et al. 2003). Neurons in both areas PIVC and VPS are multisensory as they respond not only to vestibular stimuli but also to different somatosensory, visual, and optokinetic stimuli with a preference for visual responses in area VPS. Interestingly, the human homologues of PIVC and VPS have been observed in fMRI studies to deactivate under conditions of optokinetic nystagmus (Dieterich et al. 2003). This deactivation was not observed when the OKN during optokinetic stimulation was suppressed (Dieterich et al. 1998). Taken together with our TMS results, the human data available thus suggest a general role of areas PIVC/VPS in the suppression of optokinesis.
granted that most of the target areas chosen were indeed affected by stimulation. As described above, TMS evoked clear impairments in smooth pursuit behavior some of which were expected (MT+) and others of which were nicely fitting to recently described properties of the brain regions stimulated (TPJ and CL). It should be noted, however, that such a control for the principle effectiveness of TMS was missing for the POC. The reason is that TMS had no significant influence on pursuit gain or pursuit-OKN interactions. In particular, it seems possible that the human homologue of area V6 was not affected in the present experiment by TMS given its location in the depth of the parieto-occipital sulcus (Fattori et al. 2009; Pitzalis et al. 2006, 2009; von Pforst et al. 2009) and given the just approximate knowledge of its location based on anatomical landmarks. These limitations concerning POC notwithstanding, we will suggest and argue for a final explanation why perceptual stability during pursuit eye movements could not be modified by TMS of separate brain regions. This explanation favors the view that perceptual invariances like the specific example of spatial stability addressed here is based on the activity of large and distributed neuronal ensembles employing parallel processing rather than representations offered by only small neuronal ensembles, the members of which respond in an explicit manner to just one specific concept. As a matter of fact, there is convincing evidence for distributed population coding of visual motion compensated for pursuit in the primate brain (Galletti and Fattori 2003). The so-called “real-motion” cells, that is, neurons encoding visual motion independent of pursuit eye movements, are not confined to one particular visual area, but they have been reported for areas as early as area V1 and their prevalence increases along the hierarchy of cortical processing. Specifically, the fraction of such real-motion cells amounts to around 10–15% in areas V1 and V2, increases to around 40% in area V3A and makes up the majority of neurons in area MST (for review, see Galletti and Fattori 2003). In a similar way, neuronal activity reflecting the percept of visual motion received during pursuit eye movements is also based on a large neuronal network as recently demonstrated by Dicke et al. (2008). Combining single cell recordings with psychophysical techniques in the awake behaving monkey, the authors were able to show that percept related activity was present in ~8% and 24% of V1 and MT/MST neurons, respectively, and amounted to almost 50% in area VPS. The extensive distribution of real-motion cells and percept related neurons may also explain why disturbances in motion perception during pursuit such as resulting from brain lesions and neurological disease seem to be very rare. As far as we can tell, there are indeed only 2 reports on disturbances of this faculty published in the literature so far. The first one is the presentation of a single patient with exceptional bilateral lesions of extrastriate cortex (Haarmeier et al. 1997), the second has recently demonstrated a correlation between disturbances of the ability to compensate for the visual consequences of pursuit eye movements and positive symptoms in schizophrenia (Lindner et al. 2005), likewise a condition with consequences not only for isolated brain areas but also for extended networks. Against this background, our finding that TMS of separate brain regions was not sufficient in order to induce changes in the percept is a reflection of its widely distributed neuronal substrate. Whether or not larger and more enduring lesions of specific regions such as the TPJ or the POC may impose a threat to perceptual stability during pursuit eye movements remains an open question that can be addressed in patient studies.

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References
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