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The Neural Mechanisms of the Effects of Transcranial Magnetic Stimulation on Perception

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[1]*Department of Neurological and Vision Sciences, University of Verona, Verona;* [2]*Cognitive Neuroscience Section, IRCCS San Giovanni di Dio Fatebenefratelli, Brescia; and* [3]*Department of Biomedical Sciences and Biotechnologies, National Institute of Neuroscience, University of Brescia, Brescia, Italy*

Ruzzoli M, Marzi CA, Miniussi C. The neural mechanisms of the effects of transcranial magnetic stimulation on perception. *J Neurophysiol* 103: 2982–2989, 2010. First published March 24, 2010; doi:10.1152/jn.01096.2009. Transcranial magnetic stimulation (TMS) is a technique used to study perceptual, motor, and cognitive functions in the human brain. Its effects have been likened to a "virtual brain lesion," but a direct test of this assumption is lacking. To verify this hypothesis, we measured psychophysically the interaction between the neural activity induced by a visual motion-direction discrimination task and that induced by TMS. The visual stimulus featured two elements: a visual signal (dots that moved coherently in one direction) and visual noise (dots that moved randomly in many directions). Three hypotheses were tested to explain the impairment in performance as a result of TMS: *1)* a decrease in signal strength; *2)* an induction of randomly distributed neural noise with an accompanying decrement in system sensitivity; and *3)* a suppression of relevant information processing and addition of neural noise. We provide evidence in favor of the second hypothesis by showing that TMS basically acts by adding neural noise to the perceptual process.

INTRODUCTION

Transcranial magnetic stimulation (TMS) involves delivering a brief (~300 μs) magnetic field through a coil to the head of a subject. The magnetic field induces a transitory electric current in the cortical surface under the coil causing a transynaptic depolarization of a population of cortical neurons mainly located in the superficial cortical layers. TMS has been used in many different cognitive domains to establish causality in the brain-behavior relationship. Despite its widespread use, what is lacking is an adequate theoretical framework to interpret the experimental data and to plan new protocols (Miniussi et al. 2010). The effect of TMS has often been interpreted as a transient "virtual brain lesion" (Miniussi et al. 2010; Pascual-Leone et al. 1999; Walsh and Cowey 1998), and this expression has often been considered a literal representation of the effects induced by TMS, i.e., temporary inactivation of a population of neurons. However, often the results obtained with TMS do not correspond to those predicted on the basis of lesion studies, underlining the ability of TMS to produce functional modulations rather than disruption of the neuronal activity subserving a specific behavioral task. For example, the virtual lesion theoretical framework would unequivocally predict a reduction of performance that should correlate with TMS intensity, irrespective of task difficulty. In contrast, TMS usually results in increased reaction time or decreased accuracy, neither of which correlate with stimulation intensity (Rossi et al. 2006). In other cases, performance on similar cognitive tasks is often either facilitated or inhibited by applying TMS to the same area, depending on task instructions (Harris et al. 2008a). We can find a similar circumstance with a "simple" reflex, a circuitry that most of the time involves a few neurons and that should give a stereotypical motor behavior. In some conditions, there might be a reversal in the reflex response because of the posture\state of the subject. This phenomenon is called state-dependent reflex reversal (Sherrington 1910) and has been shown also with TMS during behavioral tasks (Silvanto et al. 2008b). Such results highlight the complexity of TMS and suggest that its functional effects can be interpreted only in the context of a concomitant interaction between the characteristics of the stimulation, the anatomical\functional properties of the neural system, and its state of activation.

In a neural system, neurons that respond in the same way to a stimulus or a task will display signal correlation contributing to the final output (Stein et al. 2005), and we can define the activity of these neurons as signal. Other sources of activity that are not associated with the stimulus or task will determine the trial-to-trial response variability. Generally speaking, we can define this nonspecific activity as neuronal noise in the sense that it reflects "random" activity of neurons that is presumed to be unrelated to the encoding of behaviorally relevant variables. The ratio between these two neuronal activities will determine the signal strength necessary for the behavioral judgment. That is, the behavioral output of a system (in terms of accuracy and reaction time) is a function of the signal-to-noise ratio. In this sense, TMS could be seen to affect this relation by inducing a brief uncorrelated activity in the stimulated area. Because both signal and noise are complementary rather than mutually exclusive, TMS might affect behavior by acting on both these elements i.e., decreasing the signal strength and/or inducing random neural noise (Harris et al. 2008b; Walsh and Cowey 2000), with the direction of the effect depending on the properties (morphophysiology) of the stimulated area and on the state of activation of the system (state-dependency) (Silvanto et al. 2007, 2008b).

Harris et al. (2008b) studied TMS-induced effects on the primary visual cortex during a visual discrimination task. The subjects were asked to discriminate the orientation of visual gratings while the level of image noise in the visual stimulus was concurrently manipulated. The effect of the interaction between TMS and stimulus noise on the visual discrimination

threshold was interpreted as showing that TMS decreased signal strength without affecting neural noise.

In the light of this finding, the aim of this study was to investigate the effects of TMS with particular attention to the relationship between the induced neural activity and that underlying task execution (task-dependency). Our participants performed a motion discrimination with a random dots kinematogram (RDK) stimulus (Newsome and Pare 1988). This gave us the opportunity to interpret our data in a manner consistent with single-cell recordings and electrical stimulation in nonhuman primates and make a comparison between extent of neural activity (i.e., firing rates) of V5/MT neurons and psychophysical performance. Several studies (Bair et al. 2001; Britten et al. 1992; Masse and Cook 2008; Purushothaman and Bradley 2005; Shadlen et al. 1996) have identified a precise relationship between activity in V5/MT and motion perception performance, the so-called "linking hypotheses" (Teller 1984), suggesting that spikes that convey information about motion directional signals in V5/MT neurons are correlated with motion perceptual judgments.

Within this theoretical framework, we tested three distinct hypotheses (Fig. 1). Assuming that TMS injects electrical current into the stimulated area and its distribution selectively affects neural populations that code for the coherent motion directions, the first hypothesis predicts that TMS will lead to an overall impairment of performance through a suppression of effective signal strength. This could be represented by a parallel rightward (or leftward) shift of the psychometric curve with a change of the threshold but not of the slope of the curve. The second hypothesis states that the activity introduced by TMS will be randomly distributed (neural noise) and thus predicts a decrement in the slope of the curve representing a generalized decrement in the sensitivity of the system because of an increase in response variance (Parker and Newsome 1998). The third hypothesis postulates both signal suppression and addition of noise and thus predicts that both effects will be present.

METHODS

Subjects

Nine healthy right-handed subjects (6 males, mean age = 22 ± 3 yr), with no contraindications to TMS, participated in the experiment as paid volunteers. Visual acuity was normal or corrected to normal. All participants gave informed consent, and the experimental protocol was approved by the Ethics Committee of IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy.

Stimuli

The stimuli were presented on a computer screen with a resolution of 640 × 480 pixels and a refresh rate of 60 Hz. The stimulus was a random dots kinematogram (RDK) that covered a virtual square of 5 × 5° of visual angle, positioned at 6° to the right of the central fixation point. The RDK consisted of 300 randomly positioned white dots (1 pixel each, dot density = 12 dots/degrees^2) and lasted for ~150 ms (9 frames). The dots moved with a velocity of 6°/s. In each trial, the percentage of dots moving coherently toward the right or left varied from 1 to 50%; the remaining dots moved in random directions within the virtual square. All dots moved at the same time, but within the pattern there were two distinguishable visual elements, namely, the signal and the noise (coherent vs. random motion direction).
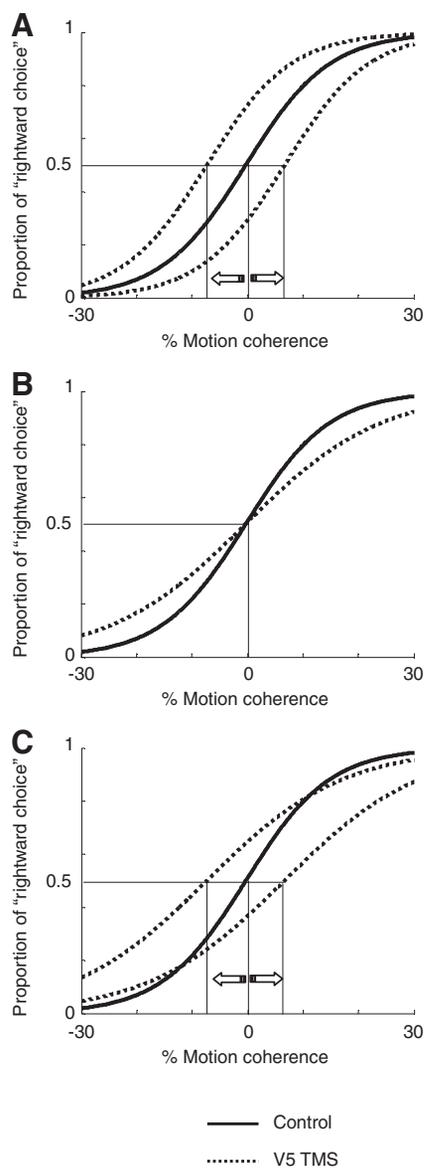

FIG. 1. Schematic representation of the 3 experimental hypotheses. Each graph shows a hypothetical subject's performance, plotting the "proportion of rightward choice" against motion coherence (negative values = leftward motion direction; positive values = rightward motion direction). *A*: hypothesis 1—transcranial magnetic stimulation (TMS) leads to an impairment of performance affecting signal strength. This prediction is graphically represented by a parallel rightward/leftward shift of the psychophysical curve representing the effect of TMS on performance with a change of the threshold point but not of the slope of the curve. *B*: hypothesis 2—TMS induces randomly distributed neural noise with a resultant decrease in the slope of the psychometric curve. *C*: hypothesis 3—both previous effects may be present as TMS acts both by suppressing relevant information processing and by adding irrelevant neural noise to the system.

Procedure

Subjects were seated in a dark room, with their chin placed on a chin rest and facing a computer monitor positioned 57 cm in front of them. They were asked to perform a discrimination task. Every trial began with a fixation cross visible at the center of the monitor for the entire trial duration. Subjects were instructed to maintain visual fixation on the cross and to press a key with the index finger as quickly as possible in response to the perceived direction of the RDK. They used the right hand to press the right key if the direction of motion was toward the right and the left hand for motion toward the left. Next, the

subjects were required to indicate their confidence in the perceived direction on a four-point scale [perceptual awareness scale (PAS); Ramsoy and Overgaard 2004; Zeki and Ffytche 1998]. The four response levels were no experience, brief glimpse, almost complete experience, and complete experience.

Each subject performed three sessions: a training session, a psychophysical session to determine the individual motion coherence threshold, and a TMS session. The TMS session included three conditions, one for each site of stimulation (see the TMS protocol below). The initial training session consisted of 90 trials. The individual's motion coherence threshold was assessed through the method of constant stimuli (total of 300 trials). On the basis of performance in this session, we chose for each subject five levels of motion coherence for which a predefined "criterion level" was reached (50, 55, 70, 75, and 90% accuracy). These coherent motion percentages were used in the TMS session (150 trials for the 3 TMS conditions explained below).

TMS protocol

TMS was applied using a Magstim super rapid magnetic stimulator (50 Hz; biphasic, 4 boosters) and a figure-of-eight coil (custom double, 70 mm; Magstim Company, Whitland, UK). The subjects wore a close-fitting skullcap on which the positions of several reference points (e.g., Cz, Oz, O1, O2 from the International 10/20 EEG system) were reproduced. Our interest was focused on V5/MT, an extrastriate visual area located in the middle temporal lobe whose neurons show response selectivity for motion direction (Britten et al. 1992; Newsome and Pare 1988; Salzman et al. 1992). Because previous studies reported that stimulation of the left hemisphere evokes phosphenes more reliably than that of the right hemisphere (Beckers and Homberg 1992; Stewart et al. 1999; but see also Silvanto et al. 2008a), the stimulation sites were on the left V5/MT, the left striate/extrastriate visual area V1/V2, and the vertex (Cz) as a control site. Before the experiment, individual target area locations were determined by a functional method; i.e., measuring the location and intensity necessary to induce stable or moving phosphenes by a single TMS pulse. This was performed starting from 5 cm lateral and 3 cm above the inion for V5/MT and 2 cm lateral and 1 cm above the inion for V1/V2. Once the target areas (V5/MT and V1/V2) were identified, they were marked on the cap as the individual subject's stimulation sites for the study. The mean coil position for left V5/MT stimulation was identified at 5.11 ± 0.69 cm lateral to the inion and 3.51 ± 0.49 cm above the inion. For left V1/V2 stimulation, the mean coil position was 2.27 ± 0.25 cm lateral to the inion and 1.96 ± 0.21 cm above the inion.

The individual phosphene threshold was established using the modified binary search (MOBS) algorithm (Tyrell and Owens 1988) for both the V5/MT and V1/V2 sites of stimulation. For both areas, the stimulation intensity used during the experiment was set to 120% of each subject's phosphene threshold. Cz stimulation intensity was the same as that used for V1/V2. The mean phosphene thresholds for V5/MT and V1/V2 were $58 \pm 12\%$ and $56 \pm 8\%$, respectively, of the maximum stimulator output. The mean intensities of stimulation for V5/MT and V1/V2 were $69 \pm 14\%$ and $67 \pm 10\%$, respectively.

For V5/MT stimulation, the coil was placed tangential to the scalp with the handle pointing toward the midsagittal axis of the subject's head. The coil was oriented vertically with the handle pointing upward for the V1/V2 location. During the experiment, the stimulating coil was fixed by means of a mechanical support that consisted of an articulated mechanical holding arm (Manfrotto Magic arm with 2 clamps) and a heavy duty tripod for all conditions. This arm allowed maximum flexibility for positioning the coil at the desired location, for selecting the appropriate orientation, and for providing maximum stability once fully positioned. During the TMS session, three TMS pulses were delivered starting 50 ms after the onset of the RDK at a frequency of 15 Hz (150 ms interpulse interval). We chose this type

of stimulation because we were not interested in mental chronometry but wanted to have a stable condition over time to test the type of effect induced by TMS over V5/MT. Moreover, the temporal parameters used were not adequate to induce a scotoma at V1/V2 level overlapping stimulus presentation (i.e., generally ~80–100 ms). The control condition was an active stimulation over Cz, a location that corresponds to a brain area that is supposedly not involved in visual processing. The order of the three locations of TMS application, i.e., V5/MT, V1/V2, and Cz stimulation, was randomized across subjects.

Statistical analysis

Signal detection theory (SDT) (Green and Swets 1966) was used to evaluate the relation between signal and noise.

A repeated-measures ANOVA was performed for each dependent variable: d' values, c values (as response criterion control) (Green and Swets 1966; Macmillan and Creelman 2005), and reaction times. Each ANOVA featured three sites of stimulation (V5/MT, V1/V2, and Cz) and five levels of motion coherence (50, 55, 70, 75, and 90% accuracy) as factors.

Logistic regression analyses were performed on data for each subject and TMS site (V5/MT, V1/V2, and Cz), using a routine for analyzing psychophysical data on MatLab (Prins and Kingdom 2009). For each subject, the routine used the maximum likelihood criterion to fit the psychometric function, and threshold slope were estimated for each subject and experimental condition. Using a parametric bootstrap procedure (Monte Carlo simulation with a number of repetitions = 400), the SE of the parameters (threshold and slope) was determined, and the goodness-of-fit (number of repetitions = 4,000) was established (Wichmann and Hill 2001a,b).

Repeated-measure ANOVAs were performed on slope values and perceptual threshold points. Tukey's HSD post hoc test was used for comparisons. For all statistical tests, the significance level was set to $P < 0.05$. The results are presented as mean and SE.

RESULTS

Signal detection analysis

An ANOVA on d' values showed a significant interaction between the two main factors: site of stimulation (V5/MT, V1/V2, and Cz) and level of motion coherence [$F(8,64) = 2.45$; $P < 0.05$]. As shown in Fig. 2, post hoc comparisons confirmed that discrimination task performance was impaired for V5/MT compared with Cz stimulation, but only for the higher levels of motion coherence ($\geq 75\%$ accuracy). Specifically, performance was impaired for the fourth and fifth levels of motion coherence. Moreover, a significant difference was found between V1/V2 and V5/MT for the fifth level of motion coherence (90% accuracy). There was no difference between V1/V2 and Cz sites of stimulation.

Repeated-measures ANOVA using c values as criterion showed a significant interaction between sites of stimulation and levels of motion coherence [$F(8,64) = 2.19$; $P < 0.05$]. Post hoc comparisons failed to show any significant differences between the three stimulation conditions within the same level of motion coherence.

Reaction time analysis

Analysis of reaction times did not show any significant statistical difference. In this experiment, we chose a level of difficulty (see threshold procedure) suitable to test accuracy rather than response time.
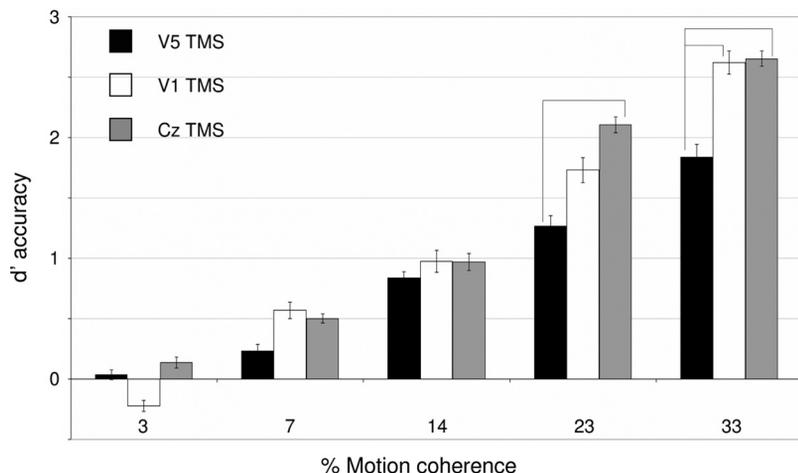
FIG. 2. Mean *d′* values (±SE) plotted for 5 levels of motion coherence. Data represent mean values across subjects. V5 TMS yields a decrement in performance only for the highest levels of motion coherence ($P < 0.05$).

Logistic regression analysis

We plotted the data in terms of "proportion of rightward choices" on the *y* axis against the percentage of motion coherence on the *x* axis. The negative values on the *x* axis indicate the percentage of coherent motion toward left direction, whereas positive values indicate coherent motion toward right direction.

A logistic regression analysis was performed for each site of stimulation and single subject to obtain the psychometric curves from the measured levels of motion coherence. For the V5/MT and Cz sites of stimulation, the goodness-of-fit was significant in all of the subjects, whereas for V1/V2, the goodness of fit failed to reach significance for one subject (S_12).

A repeated-measures ANOVA on slope data with site of stimulation as a factor showed a statistically significant difference [$F(2,16) = 4.92$; $P < 0.05$]. Post hoc comparisons showed that administering TMS at V5/MT site led to a decrement in the slope of the psychometric curves as compared with the Cz, and to V1/V2 sites of stimulation.

A repeated-measures ANOVA on perceptual threshold points with site of stimulation as a factor failed to reach

significance. These results are shown in Fig. 3 as group fitting and in Fig. 4 as individual plotting for each subject.

To verify that the decrement in the slope for the V5 TMS condition was not related to spurious correlation, we compared the two-parameters model against a single parameter model in each subject. This was done for V5 TMS and Cz TMS, allowing a changing of the threshold, followed by a forced slope to be identical between conditions. A single threshold was estimated for both the psychometric curves, assuming that the threshold was not different for the two data sets. Thus we were able to test the effective weight of the slopes on the goodness-of-fit (i.e., 1 model parameter). This analysis showed that the slope decrement was not caused by a spurious correlation, because the goodness-of-fit in the slope one-model parameter was worst than the two-parameters model for all but two subjects (77.78%) (Wichmann and Hill 2001a,b).

Perceptual awareness scale

Finally, a repeated-measures ANOVA was performed with the following factors: site of stimulation, levels of motion coherence, and PAS ranks. A significant interaction between
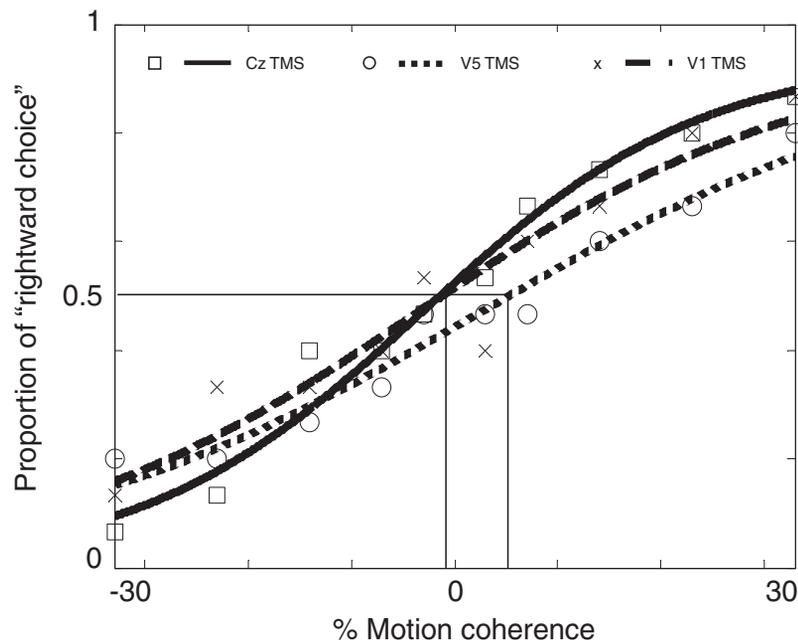

FIG. 3. Logistic regression group analysis for 3 TMS conditions (V5, V1/V2, and vertex-Cz). V5 TMS induced a decrement in the slope of the curve compared with V1/V2 and Cz TMS ($P < 0.05$), indicating a generalized reduction in system sensitivity. Although a rightward shift in the threshold point following V5 TMS seems to be present, statistical analysis failed to reach significance.
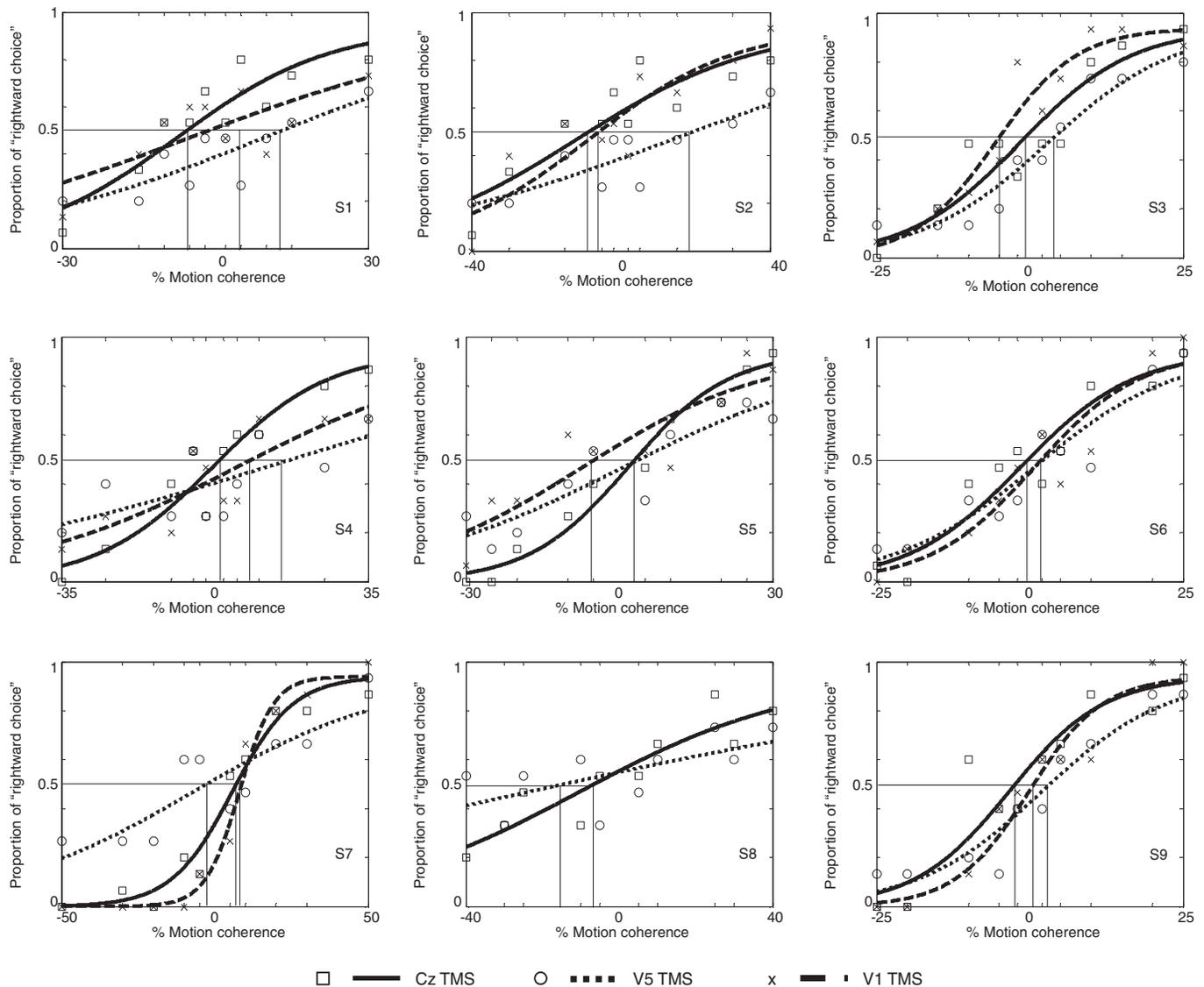
FIG. 4. Single subjects data for 3 TMS conditions (V5, V1/V2, and vertex-Cz). Squares are associated to Cz data points and solid lines represent Cz TMS fitting. Circles indicate V5 TMS data points, dotted lines are V5 TMS fittings, crosses indicate the V1 data points, and dashed lines represent V1/V2 fittings. For S8, the goodness-of-fit in the V1/V2 TMS condition failed to reach significance.

levels of motion coherence and PAS ranks was found [$F(12,96) = 16$; $P < 0.01$], but there was no interaction between sites of stimulation and PAS ranks. Accordingly, increasing motion coherence tended to increase perceptual awareness of direction, but no differential effects of TMS were detected.

DISCUSSION

In brain stimulation studies involving perception and cognition, TMS may modify the signal-to-noise ratio of highly organized neural activity, and this often (but not always) results in impairment of the subject's performance. In principle, these changes in performance may be caused by a reduction in the strength of the neural signal (Harris et al. 2008b), an increase in neural noise in the stimulated area (Walsh and Cowey 2000), or both. In this study, we tested these hypotheses by studying the effect of TMS on the shape of the psychometric function in a visual motion discrimination task.

The results showed that administering TMS over V5/MT leads to a decrement in motion discrimination performance with above-

threshold stimuli. This means that only with high levels of coherence (or low levels of noise) it is possible to observe the effect of TMS on the neural population activity that code for the relevant information and therefore on behavior. The impairment in task performance was not associated with a rightward (or leftward) shift in the psychometric function, suggesting that TMS does not reduce the strength of the neural signal in a direction discrimination task. Because the intensity of the signal arises from the interaction between two factors, namely, firing rate and number of neurons activated by the stimulus, a reduction in signal strength would have been caused by a reduction/suppression of the activity of the neural population that code for the "relevant information" (i.e., signal), therefore reducing the strength of the behavioral response. This might be the consequence of an alteration in membrane permeability induced directly by TMS, or more likely, of a TMS enhancement of the inhibitory GABAergic activity (Mantovani et al. 2006; Moliadze et al. 2003).

However, this was not the case, and what we observed was a decrease in the slope of the psychometric function for the

same stimulation site, indicating increased neural noise in the system and a reduction of its sensitivity as a consequence of an increase in response variance. Thus these results are in agreement with our second hypothesis that TMS acts by increasing neural noise in the stimulated area.

The lack of significant differences in terms of perceptual awareness indicates that TMS affects only the perceptual ability to discriminate motion direction rather than higher cognitive mechanisms such as perceptual consciousness, decision-making, or response selection and execution. This lack of modifications suggests that the TMS effect is highly specific for the task, i.e., motion direction discrimination, which engages a specific site, i.e., the stimulated (V5/MT) area, instead of a downstream area. No significant differences were found for V1/V2 TMS, despite the anatomical and functional interconnections between V1/V2 and V5/MT. Therefore we assume that the task used here is specifically subserved by V5/MT and so are the TMS effects.

Because we cannot interpret these results without referring to the stimulated area, it is important to note that neurons in V5/MT show response selectivity in terms of visual motion direction coding (Britten et al. 1992; Newsome and Pare 1988; Salzman et al. 1992), and these neurons are organized in different clusters on the basis of their preferred motion direction (Albright et al. 1984; Krug 2004; Zeki 1974). Several studies (Bair et al. 2001; Britten et al. 1992; Masse and Cook 2008; Purushothaman and Bradley 2005; Shadlen et al. 1996) have identified a close relationship between neural activity in V5/MT and motion perception, suggesting a correlation between activity of V5/MT neurons and motion perceptual judgments (Teller 1984). In a microstimulation study, Murasugi et al. (1993) found that microstimulation of a precise V5/MT neural column that coded for the preferred motion direction led to an increase in the number of responses in the preferred direction as a result of injection of coherent motion signal in the congruent direction. However, when the amplitude of the electrical current was increased, the slope of the psychometric function related to V5/MT stimulation also changed. Increasing the amplitude of the electrical current could be associated with an increase in the dimension of the stimulated area and number of stimulated neurons, therefore suggesting an activation of further neurons that coded for other motion directions different from the preferred one (Murasugi et al. 1993). In other words, increasing the amplitude of the electrical current produced an increase in not only the signal but also in the neural noise.

Returning to TMS studies, it seems logical to conclude that specific neural activity in the V5/MT area correlates with a subject's performance and that modifying that activity by TMS should yield modification of the subject's behavioral performance. Because our aim was to find a link between behavioral TMS studies and physiology, through a psychophysical approach, we applied the same rationale as that used in studies with electrical microstimulation of a monkey's V5/MT region. We believe that electrical microstimulation and single-cell recording combined with psychophysics provides the best framework to interpret our data because TMS, as microstimulation, essentially induces an electrical current flow in the cortex. Obviously, there are differences between the two techniques: the spatial resolution of TMS is indeed lower and therefore no specificity on the stimulated neural population can

be claimed. Nevertheless our results corroborate those from electrical microstimulation experiments when an increase of the amplitude of the electrical current is used, and thus a larger area is stimulated with a consequent lower spatial resolution. In the same way, it is likely that magnetic stimulation would affect all neural populations, i.e., both neurons that code for coherent motion directions and those that code for all the others motion directions (that with respect to the task can be defined as random) within the stimulated cortical area. Thus TMS induces neuronal activity that adds itself to the ongoing neural activity that can be considered both as noise and as part of the signal depending on the neuronal population stimulated. In this way, TMS could generate neural activity (noise) with respect to the relevant information carried by the stimulated area (signal). Therefore TMS seems to influence both those neurons that code for nonspecific responses, i.e., noise, and those that code for coherent motion, i.e., signal, but the behavioral outcome depends on the interaction with the ongoing neural activity (task-dependency).

At the neural level, we speculate that, in the case of motion coherence under perceptual threshold or near-threshold, the level of activity for both the neural populations involved in the task (coherent motion direction and random motion directions) is not at maximum level, and TMS excites approximately the same number of neurons in both neural populations. As a result, the general level of activation is increased, but the signal-to-noise ratio remains the same as in control condition and therefore performance is unaffected. In contrast, when motion coherence is above the perceptual threshold, the signal-to-noise ratio induced by visual stimulation is higher, leading to a good level of performance (90% of accuracy in our experiment). In this activation state, TMS mainly excites the neural populations that are less active in that moment, namely, those that code for random (e.g., others) motion directions. In this way, performance is impaired because the signal-to-noise ratio decreases.

TMS has been shown to elicit distinct and complex episodes of enhanced and suppressed activity at the cortical level (Allen et al. 2007; Moliadze et al. 2003), also depending on the state of the stimulated area (Pasley et al. 2009). Considering the findings from neuronal recording during TMS, which reported a increase in the number of neuronal spikes soon after TMS (Allen et al. 2007; Moliadze et al. 2003), it is possible that TMS produces a sudden and strong synchronized neuronal discharge, corresponding to the activation of the neural populations entrained by the electric field (Veniero and Miniussi 2008), that will alter the signal-to-noise ratio. Increasing neural noise therefore will increase the amount of neurons that code for other information and decrease performance. This initial neural activation is generally followed by a reduction of activation in the stimulated site that can temporary alter further neural communications with the connected areas.

These results are not in agreement with the study of Harris et al. (2008b). However, a direct comparison between these two studies should be taken with caution because the stimulated area (V1/V2 vs. V5/MT) and the TMS parameters used (single pulse TMS vs. rTMS) are different. Moreover, in Harris et al. (2008b), an equivalent noise paradigm was used (Dakin et al. 2005; Pelli and Farell 1999) that allowed an analysis of the perceptual threshold as a function of visual noise through a staircase procedure. In this study, the rationale was different

because we were interested in the effects of TMS as a function of motion coherence and not only on the absolute threshold point.

Finally, regarding the conditions that determine the characteristics of the TMS effects at cortical level, together with anatomical and neurophysiological factors, one should include more basic stimulation parameters. These concern the intensity, frequency of stimulation, the orientation, shape, and dimension of the coil (focality and depth of stimulation), the timing and duration of stimulation, and the possible interactions between these factors (Rossi et al. 2009; Wassermann et al. 2008). The definition of the methodological variables in a "brain-oriented" structure, i.e., to define the parameters of stimulation on the basis of the effects that can be induced in a given system, can lend strong support to the final interpretation of the data.

In conclusion, data modeling using logistic psychometric function showed that TMS increases neural noise in the stimulated area, and, as a consequence, in our task induced a decrement in the slope of the psychometric function. Together, these results suggest that, through a psychophysical approach, it is possible to highlight the functional activation state of the target area and to determine the specificity of the behavioral effects in the context of TMS administration. Traditionally, applications of TMS have focused on characterizing the relationships between cortical areas and behavior and to trace the temporal course of the activity of a particular cortical region that contributes to a given task. However, there are limits to how much knowledge can be gained from cognitive states by examining this relationship in isolation from the functional effects induced by TMS. With a more precise definition of the mechanisms of action of TMS, theoretical interpretation of TMS data can extend beyond the simple relationship between an anatomical area and behavioral impairment.

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