

Juha Silvanto, Zaira Cattaneo, Lorella Battelli and Alvaro Pascual-Leone
J Neurophysiol 99:2725-2730, 2008. First published Mar 12, 2008; doi:10.1152/jn.01392.2007

You might find this additional information useful...

This article cites 38 articles, 11 of which you can access free at:

<http://jn.physiology.org/cgi/content/full/99/5/2725#BIBL>

Updated information and services including high-resolution figures, can be found at:

<http://jn.physiology.org/cgi/content/full/99/5/2725>

Additional material and information about *Journal of Neurophysiology* can be found at:

<http://www.the-aps.org/publications/jn>

This information is current as of June 27, 2008 .

Baseline Cortical Excitability Determines Whether TMS Disrupts or Facilitates Behavior

Juha Silvanto,¹ Zaira Cattaneo,^{1,2} Lorella Battelli,¹ and Alvaro Pascual-Leone¹

¹Berenson-Allen Center for Noninvasive Brain Stimulation, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Massachusetts; and ²Department of Psychology, University of Pavia, Piazza Botta, Italy

Submitted 23 December 2007; accepted in final form 4 March 2008

Silvanto J, Cattaneo Z, Battelli L, Pascual-Leone A. Baseline cortical excitability determines whether TMS disrupts or facilitates behavior. *J Neurophysiol* 99: 2725–2730, 2008. First published March 12, 2008; doi:10.1152/jn.01392.2007. Transcranial magnetic stimulation (TMS) is increasingly used to modify brain activity noninvasively and to study brain-behavior relations. However, results can be variable and the conditions that affect the functional efficacy of TMS remain unclear. Here we show that on-line TMS can either facilitate or suppress perceptual functions depending on the baseline level of activity of the targeted brain region. When TMS was applied over the motion selective region V5/MT during a simple motion-detection task, subjects' motion-detection ability was impaired. Similarly, suppression of V5/MT activity using off-line 1 Hz repetitive TMS (rTMS) disrupted performance in a subsequent motion-detection task. However, paradoxically, on-line V5/MT TMS had a facilitatory effect on motion detection if V5/MT had been suppressed by off-line 1-Hz rTMS prior to the motion-detection task. These results demonstrate that TMS can have an unexpected facilitatory effect on behavior when the targeted neural population is in a suppressed state. Our findings provide further evidence for the view that the effects of TMS are modulated by the initial activation state of the targeted neural population.

INTRODUCTION

Transcranial magnetic stimulation (TMS) allows the study of the neural basis of cognitive functions in neurologically intact subjects (Cowey 2005; Walsh and Pascual-Leone 2003) and may potentially offer therapeutic potential in a number of neurological and psychiatric conditions (e.g., Kobayashi and Pascual-Leone 2003; Ridding and Rothwell 2007). Despite its increasingly wide use, the mechanisms through which TMS influences behavior remain poorly understood. Animal studies (Moliázde et al. 2003; Valero-Cabre et al. 2006, 2007) and modeling approaches (Wagner et al. 2007) have begun to provide insights into the biological effects of TMS in human subjects, but so far these findings have not been linked to behavioral consequences of TMS. One potentially important factor in understanding the mechanisms of TMS involves the impact of the initial activation state of the stimulated region on the efficacy of stimulation. Studies on the impact of repetitive TMS on corticospinal excitability suggest that the baseline level of excitability of the targeted motor cortex may critically influence the results. For example, Siebner et al. (2004) showed that when the excitability level of the corticospinal projection is increased using transcranial DC stimulation

(tDCS), a subsequent period of 1-Hz repetitive TMS (rTMS) leads to a lasting *reduction* in corticospinal excitability. Conversely, when corticospinal excitability is reduced prior to application of rTMS, the same 1-Hz rTMS causes a sustained *increase* in corticospinal excitability.

The extent to which the initial cortical activation state modulates the effects of *on-line* TMS (the neural effects of which are different from those induced by rTMS) (cf. Ridding and Rothwell 2007) is not known. Furthermore the behavioral consequence of the interaction between the baseline cortical activation state and the application of TMS has so far not been investigated. This is an important issue for the use of TMS in basic research as well as for its efficacy as a therapeutic tool. For example, when off-line rTMS is used to determine the necessity of cortical regions in cognitive functions, differences in the initial cortical activation state caused by seemingly irrelevant factors (such as whether the subject is resting or speaking with the experimenter) during the application of rTMS may affect the efficacy of stimulation. For the therapeutic use of TMS, this issue is also important as neurological disorders are often associated with abnormal levels of cortical excitability; for example, depression has been linked with hypoactivity in the left dorsolateral prefrontal cortex (DLPFC) and hyperactivity in the right DLPFC (Cummings 1993). Effective use of TMS thus requires an understanding of how the initial cortical activation state may modify its effects.

In the present study, we explored how the baseline activation state of the targeted brain region influences the behavioral impact of TMS. Specifically we determined whether the application of *off-line* 1-Hz rTMS to suppress neural activity in the motion area V5/MT prior to performing a motion-detection task modulates the effects of *on-line* V5/MT TMS applied during that task. Our results show that on-line TMS over V5/MT can either facilitate or impair motion detection depending on the initial activation state of V5/MT.

METHODS

Subject

Eight subjects (6 males and 2 females, aged 24–37 yr), including author J.S., took part in the experiment. Informed consent was obtained from all subjects. The experiment was approved by a local ethics committee, and subjects were treated in accordance with the declaration of Helsinki.

Address for reprint requests and other correspondence: J. Silvanto, Berenson-Allen Center for Noninvasive Brain Stimulation, Harvard Medical School and Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (E-mail: jsilvanto@bidmc.harvard.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Visual stimulus

The stimuli were presented on a 15-in (800 × 600 pixels) monitor. Viewing distance was 57 cm. The global motion stimulus consisted of 100 white dots (1 pixel each), placed at random positions within an imaginary square subtending $1.5 \times 1.5^\circ$ of visual angle and moving coherently to either right or the left within the virtual square on a black background. The displacement of the dots on motion trials was 1 pixel/frame such that they moved with a velocity of $3^\circ/s$. On “no-motion” trials, the dots were stationary. Each trial began with a fixation point appearing in the middle of the screen for 500 ms followed by a blank screen for 300 ms after which the stimulus appeared. Stimulus duration was 40 ms (or 4 frames lasting for 10 ms each). Subjects were required to report whether or not they detected motion in the display. After subjects had given their responses, a blank screen appeared for 1,000 ms before the start of the next trial.

To obtain a stable level of performance, subjects were given practice blocks prior to testing. If direction discrimination performance was $>90\%$, one frame was removed from the stimulus, and if performance was $<70\%$, one frame was added to the stimulus. Five of the subjects performed the task with three frames and three subjects with four frames. Each block consisted of 40 trials of which 20 were motion trials (10 leftward motion, 10 rightward motion) and 20 were no-motion trials. All three types of trials were intermixed randomly within a block.

Transcranial magnetic stimulation

TMS was delivered by means of a Magstim Super Rapid machine (Magstim) via a 70-mm figure-eight coil. V5/MT was located using the functional method of inducing moving phosphenes (Stewart et al. 1999; see Walsh and Pascual-Leone 2003 for detailed discussion), a technique that has been used in a number of studies on V5/MT function (e.g., Campana et al. 2002; 2006; Pascual-Leone and Walsh 2001; Silvanto et al. 2005). In this procedure, phosphenes are induced from each point in a 3×3 cm grid around a central point of 3 cm dorsal and 5 cm lateral from theinion, and the site from which the most vivid moving phosphenes are induced is defined as V5/MT. Stimulation of this region has been shown to disrupt motion perception in a large number of studies (e.g., Hotson and Anand 1999; Matthews et al. 2001). Vertex was used as a control site in the experiment to control for the nonspecific effects of TMS (both the V5/MT TMS and vertex TMS induce auditory and sensory artifacts such as clicking sounds and tapping sensation on the scalp, so a statistical difference between these conditions cannot be due to these factors). The mean scalp coordinates were 3.5 cm dorsal and 5.67 cm lateral from theinion. V5/MT in the left hemisphere was stimulated in all participants because it has consistently been found to produce phosphenes more reliably than the right hemisphere (Antal et al. 2001; Beckers and Hömberg 1992; Stewart et al. 1999). In three subjects, double pulses were used (as moving phosphenes could not be induced with single pulses of TMS). Mean phosphene threshold (with single-pulse TMS) measured using the binary search paradigm (Tyrrell and Owens 1988) was 65.75 ± 7.76 (mean \pm SD) of the maximum stimulator output.

TMS conditions

The objective of this study was to determine whether suppressing V5/MT using off-line 1-Hz TMS prior to performing a motion-detection task modulates the behavioral effect of on-line V5/MT TMS applied during that task. This was achieved by running two motion-detection experiments with both experiments preceded by one kind of off-line rTMS. In the critical manipulation, the initial activation state of V5/MT was altered with off-line rTMS prior to the motion-detection experiment. For the baseline condition, off-line rTMS was applied over the vertex prior to the motion experiment. Off-line rTMS

was applied for 10 min at a stimulation frequency of 1 Hz; these stimulation parameters have been shown to suppress cortical activity (e.g., Gerschlagler et al. 2001; Maeda et al. 2000; O’Shea et al. 2007) and to induce significant disruptions in various psychophysical paradigms (e.g., Grossman et al. 2005; Hilgetag et al. 2001).

To control for nonspecific effects of on-line TMS, vertex was used as the control site against which the behavioral impact of on-line V5/MT TMS was compared. There were therefore two off-line rTMS conditions (with rTMS applied over either V5/MT or the control site, vertex, prior to the motion-detection task) and two on-line TMS conditions (with TMS applied over either V5/MT or vertex during the motion task). The critical question was whether the disruptive behavioral effect of on-line V5/MT TMS on motion detection (assessed relative to the control condition, the on-line Vertex TMS condition) was affected by the preceding off-line V5/MT rTMS. TMS was applied at an intensity of 60% of maximum stimulator output. A single intensity was used for all subjects (for both on- and off-line TMS) on the basis of several previous studies (Muggleton et al. 2006; O’Shea et al. 2004; Pitcher et al. 2007; Silvanto et al. 2005, 2007b). No subject reported the impression of phosphenes during the motion-detection task.

Each subject completed a total of four blocks of trials of the motion-detection task following the off-line rTMS. During two of the blocks of the motion-detection task, on-line TMS was applied to V5/MT, whereas during the other two blocks, on-line TMS was applied over the vertex. The order of these four blocks was counter-balanced. On-line TMS consisted of a short train of three pulses (pulses applied at 20 Hz; i.e., pulse gap of 50 ms) that began 50 ms after stimulus onset on each trial (this delay was chosen on the basis of estimates that it takes ~ 50 ms for motion information to reach V5/MT) (Raiguel et al. 1995). To rule out the possibility that vertex TMS had a behavioral effect, two blocks without any TMS were also run, one before the application of Off-line rTMS and the other an hour after its completion.

Procedure

At the beginning of the first session, subjects’ V5/MT region was localized after which the subjects were thresholded for the behavioral task. Figure 1 shows the timeline of an experimental session. The session began with a no-TMS block, followed by application of off-line rTMS either over V5/MT or vertex for 10 min. Immediately after the off-line rTMS the motion-detection experiment was run (consisting of 4 blocks of trials; 2 blocks with on-line V5/MT TMS and 2 blocks with on-line vertex TMS). After a 50-min break (~ 1 h after the completion of the off-line rTMS), a further no-TMS block was run. This procedure was then repeated for the second off-line rTMS site on the following day.

RESULTS

We performed a signal-detection analysis (Green and Swets 1966) on the data to obtain measures of subjects’ sensitivity (d') and bias (beta) in the motion-detection task.

Figure 2 shows subjects’ motion-detection sensitivity (d') in the on-line V5/MT and vertex TMS conditions as a function of whether the preceding off-line rTMS was applied over V5/MT or vertex. A 2×2 ANOVA with off-line rTMS sites (V5/MT, vertex) and on-line TMS sites (V5/MT, vertex) as main factors indicated a significant interaction [$F(1,7) = 51.23$; $P = 0.0002$].

Pairwise comparisons were carried out with the required P value adjusted with the Bonferroni correction (adjusted P value = 0.0125). These comparisons revealed that, as expected, on-line V5/MT TMS impaired motion-detection per-

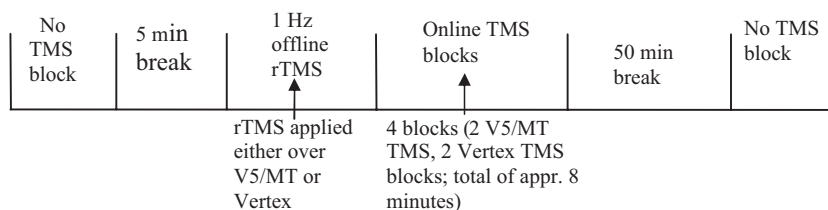


FIG. 1. Timeline of the experiment. Each session began with a no transcranial magnetic stimulation (no-TMS) block. This was followed by the off-line 1-Hz repetitive TMS (rTMS) procedure that was applied over either V5/MT or the control site (vertex). After the off-line rTMS procedure, a motion-detection experiment was carried out in which on-line TMS was applied either over V5/MT or the vertex on each trial. This experiment consisted of a total of 4 blocks of 40 trials (2 blocks with on-line V5/MT TMS and 2 blocks with on-line vertex TMS), the order of which was counterbalanced. A 2nd no-TMS block was run 50 min after the completion of the TMS blocks. The V5/MT and the vertex 1-Hz TMS were carried out on separate days.

formance when the initial activation state of V5/MT had not been suppressed prior to the experiment: after off-line vertex rTMS (i.e., the control off-line rTMS site), on-line TMS applied over V5/MT impaired motion-detection performance relative to on-line TMS applied over the vertex [$t(7) = 4.683$; $P = 0.002$]. Off-line rTMS applied over V5/MT also significantly impaired motion-detection performance: detection accuracy in the on-line Vertex TMS condition (i.e., the control on-line TMS condition) was lower after off-line V5/MT rTMS than after off-line vertex rTMS [$t(7) = 3.489$; $P = 0.010$].

Critically, after off-line V5/MT rTMS, on-line TMS applied over V5/MT *facilitated* motion-detection performance relative to on-line Vertex TMS [$t(7) = 5.015$; $P = 0.002$]. Furthermore, motion-detection performance with on-line V5/MT TMS was significantly higher after off-line rTMS to V5/MT than after off-line rTMS to vertex [$t(7) = 5.248$; $P = 0.003$]. These comparisons show that on-line V5/MT TMS improves motion-detection performance if V5/MT is in a suppressed state (i.e., after application of off-line V5/MT rTMS).

To determine whether the combination of off- and on-line vertex TMS was a valid control condition, motion-detection performance in the no-TMS condition was compared with subjects' performance in the condition in which both off- and on-line TMS was applied over the vertex. There was no statistical difference between these conditions [$t(7) = 0.406$; $P = 0.696$]. This demonstrates that vertex TMS had no significant effect on motion-detection performance and that this site was a valid control.

TMS did not significantly influence subjects' response bias. A 2×2 ANOVA revealed no significant interaction [$F(1,7) = 1.37$; $P = 0.280$] nor main effects [$F(1,7) = 0.88$; $P = 0.379$; $F(1,7) = 0.2$; $P = 0.668$] were observed. The mean values for each condition are: off-line vertex TMS/on-line V5/MT TMS: 3.91; off-line vertex TMS/on-line vertex TMS: 5.86; off-line V5/MT TMS/on-line V5/MT TMS: 4.57; off-line V5/MT TMS/on-line vertex TMS: 4.37.

Control experiments

It could be argued that it is the difficulty of the motion task (rather than the initial activation state of V5/MT) that determines whether on-line V5/MT impairs or facilitates behavior. This is logically possible given that subjects' performance in the baseline condition (i.e., on-line vertex TMS condition) was lower after off-line V5/MT rTMS than after off-line vertex rTMS (the mean values for motion-present trials were 69.6 and 81.25%, respectively). To rule out the possibility that on-line V5/MT TMS facilitates performance when detection accuracy is low, we determined the effects of on-line TMS (without prior 1-Hz rTMS) when the motion task was more difficult. Five subjects (who had all taken part in the main experiment) took part in this control experiment. Subjects were thresholded for a motion-detection accuracy of 60–70%, using the procedure described in the preceding text. The visual stimuli and TMS parameters were identical to those used in the main experiment. Vertex was stimulated as the control site. Six

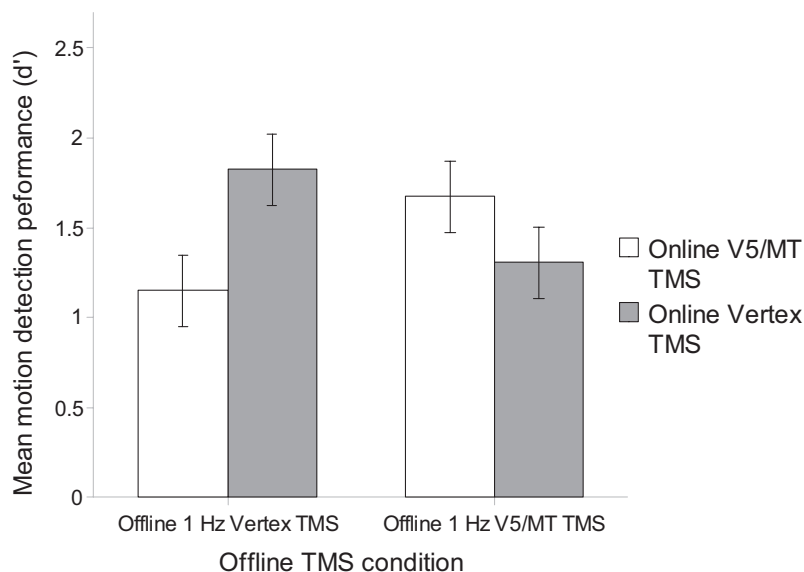


FIG. 2. Subjects' mean ($n = 8$) performance (d') in the motion-detection task. On-line V5/MT TMS had the expected disruptive effect on motion detection (relative to on-line vertex TMS that was used as the control condition) when the motion-detection task was preceded by the control (vertex) 1-Hz TMS. In contrast, on-line V5/MT TMS facilitated motion-detection performance relative to on-line vertex TMS when the motion-detection task was preceded by 1-Hz V5/MT TMS. The error bars indicate ± 1 SE.

blocks (as described in METHODS) were run (2 blocks for on-line V5/MT TMS, 2 blocks from on-line vertex TMS and 2 no-TMS blocks) the order of which was counterbalanced.

On-line V5/MT TMS induced a significant disruption in motion detection relative to the no-TMS and the vertex TMS conditions. Mean motion-detection accuracies for the three conditions were: no-TMS, 68.5%; vertex TMS, 68%; V5/MT TMS, 58.3%; pairwise comparisons: V5/MT TMS vs. no-TMS, $P = 0.009$; V5/MT TMS vs. vertex TMS: $P = 0.011$; no-TMS vs. vertex TMS: $P = 0.846$). The finding that on-line V5/MT TMS disrupted motion-detection performance even when the motion-detection task was made more difficult rules out the possibility that the difficulty of the psychophysical task alone determines whether TMS disrupts or facilitates behavior.

To determine whether 1-Hz TMS as used in the present study was successful in suppressing V5/MT activity, an additional control experiment was carried out. In this control experiment, 1-Hz TMS was applied over the V5/MT location that was stimulated in the main experiment, and subjects' phosphene thresholds were measured before, immediately after, and 1 h after the 1-Hz TMS. All eight subjects from the main experiment took part. The mean PTs (as percentage of maximum stimulator output) were: before 1-Hz TMS: 66.13 ± 6.85 ; immediately after 1-Hz TMS: 74.75 ± 10.47 ; 1 h after 1-Hz TMS: 66.3 ± 5.6 . A paired-sample *t*-test confirmed that the PT immediately after the 1-Hz TMS was significantly higher than that measured before the 1-Hz TMS ($P = 0.001$), demonstrating that 1-Hz TMS as used here significantly decreases the excitability of V5/MT. The V5/MT PT values measured prior to the main experiment did not statistically differ from the pre 1-Hz PT values in this control experiment ($P = 0.43$).

DISCUSSION

Our results show that on-line TMS applied over the motion area V5/MT can either suppress or facilitate motion detection depending on the initial activation state of this region. Consistent with a large number of studies (see Cowey 2005; Walsh and Pascual-Leone 2003 for reviews), TMS applied on-line over V5/MT during a motion-detection task impaired subjects' performance; similarly, suppression of V5/MT activity with off-line rTMS impaired subsequent motion detection. Paradoxically, on-line V5/MT TMS had a facilitatory effect on motion detection when this region had been suppressed with off-line rTMS prior to the motion-detection task. Effectively, the on-line V5/MT TMS (that on its own disrupted motion-detection performance) removed the behavioral impairment induced by the off-line rTMS to V5/MT. The finding that on-line TMS, which under uncontrolled circumstances impairs behavior, can paradoxically improve performance when the targeted region is in a suppressed state of activity, demonstrates the importance of the initial activation state in determining the behavioral impact of TMS.

The supraliminal motion stimulus in our study was likely to cause excitatory suprathreshold postsynaptic potentials (EPSPs) in a small population of neurons preferring the direction of motion and subthreshold EPSPs in those preferring other directions of motion; this differential activation enables V5/MT to detect the presence of motion. On-line TMS as used here is likely to primarily excite neurons (Moliazde et al.

2003), and it was thus likely to turn the subthreshold activity of neurons not strongly driven by the motion stimulus into suprathreshold activation. In contrast, the excitatory influence of on-line TMS on neurons tuned to the present stimuli is less significant as these neurons are already suprathreshold. As neurons tuned to the motion stimulus are no longer preferentially activated relative to the neurons not tuned to the presented motion, motion detection is impaired. This explanation is consistent with our recent proposal on how the state-dependency of TMS can explain its behavioral and perceptual effects (cf. Silvanto and Muggleton 2008a,b).

When TMS is applied off-line to suppress neural activity, all neural populations become less excitable causing the activation induced by the motion stimulus to be below perceptual threshold. Although neurons tuned to the presented motion direction are likely to be more active than neurons not tuned to the motion stimulus, their activation is likely to be below the threshold required for motion detection. In this case, with on-line TMS, the subthreshold activity of neurons tuned to the motion stimulus becomes suprathreshold. The activation of neurons not tuned to the presented motion is also enhanced, but not to a suprathreshold level, as these neurons are initially less strongly activated by the motion stimulus. Therefore on-line TMS (when applied over suppressed V5/MT) restores the differential activation of neural populations associated with motion perception. Interestingly, on-line V5/MT TMS (when applied after off-line V5/MT TMS) did not facilitate motion detection beyond the performance found in the control condition when both off- and on-line TMS were applied over the vertex. This may indicate that on-line TMS cannot specifically recruit neurons in that network preferring the presented motion direction but push to perceptual threshold the neurons that had become subthreshold due to the off-line TMS.

It is possible that 1-Hz rTMS applied over the V5/MT region impaired motion detection by suppressing the reciprocal connections between V1 and V5/MT. Recurrent interactions between these regions, and in particular feedback projections from V5/MT to V1, have been shown to be necessary for conscious perception of visually presented motion (Silvanto et al. 2005). This possibility is supported by a recent study in which functional magnetic resonance imaging (fMRI) was used to determine the neural correlates of behavioral impairments in a visuospatial task induced by parietal TMS (Sack et al. 2007). Neural activity changes correlating with the impairment were observed in both the directly stimulated parietal as well as remote ipsilateral frontal brain regions that are normally functionally connected during the execution of the behavioral task. This suggests that it may be important to take into account the distal effects of TMS when explaining the neural basis of behavioral impairments induced by this technique. From our behavioral findings, it is impossible to infer whether it was the modulation of V5/MT or its connections with V1 that was responsible for the present results.

The role of the baseline activation state in determining the behavioral impact of TMS has been previously studied by using visual adaptation to suppress neural populations of specific tunings within the stimulated region (Silvanto and Muggleton 2008a,b; Silvanto et al. 2007a). That work showed that TMS interacts with the activity imbalance between distinct neural populations induced by visual adaptation, perceptually facilitating neurons that have been made less active/excitable

by adaptation. The present study differed from the previous work in that the objective was not to selectively suppress specific neural populations but to induce a uniform suppression of *all* neurons within the stimulated region. This is an important difference as the finding that a uniform suppression of a cortical region reverses the behavioral effects of on-line TMS demonstrates that the state-dependency of TMS is not dependent on the presence of an activity imbalance between functionally distinct neural populations. Rather these findings show that it is the absolute activity state of neurons (rather than their activity state *relative to other neurons* in the stimulated region) that determines the effect of TMS.

In addition to revealing some of the factors that modulate the behavioral efficacy of TMS, these findings have implications for the therapeutic applications of this technique. When designing a treatment protocol, it is important to have an understanding of the activity state of the regions affected by the neurological condition as this will determine the behavioral impact of TMS. The real-time combination of TMS with electroencephalography (EEG) may be valuable in this context as EEG might be used to trigger the TMS and thus assure consistent timing of the TMS stimuli with a given state of cortical activation. This may have implications for the use of TMS in disorders such as epilepsy. Valentin et al. (2007) have shown that EEG responses to TMS can identify epileptogenic cortex and may substantially improve the diagnosis of focal epilepsy, particularly if combined with standard EEG studies. In this study, waveforms resembling interictal epileptiform discharges occurred when stimulating the epileptogenic side of patients but not of normal subjects. Given that the effects of TMS seem to be state-dependent, it may be possible to use TMS to suppress neural activity at the onset of such waveforms and thus prevent epileptic seizures.

The present findings are also related to studies carried out in individual suffering from migraine. In a study by Brighina et al. (2002), 1-Hz rTMS over the occipital cortex led to a significantly increased visual cortex excitability expressed as a decrease in PT in subjects affected by migraine with aura. Conversely, after a 1-Hz TMS train, normal subjects showed increased PT values, suggestive of a decrease in visual cortex excitability. Similar findings have been obtained in normal subjects by using light deprivation to modulate the excitability of the visual cortex prior to induction of phosphenes by TMS (Brighina et al. 2005).

The static trials in our psychophysical task consisted of stationary dots (as opposed to noncoherently moving dots). It is therefore possible that even if participants did not detect coherent motion per se, they could detect the presence of motion by the temporal modulation in the visual stimulus. If this is the case, TMS in the present study altered motion-detection performance by modulating flicker sensitivity. Future studies are required to study the state-dependency of TMS effects on motion perception in more detail.

In conclusion, our results show that the behavioral effects of TMS are dependent on the excitability of neurons in the stimulated region, demonstrating the importance of the initial activity state in modulating the efficacy of TMS.

REFERENCES

- Antal A, Nitsche MA, Paulus W.** External modulation of visual perception in humans. *Neuroreport* 12: 3553–3555, 2001.
- Beckers G, Hömberg V.** Cerebral visual motion blindness: transitory akinetopsia induced by transcranial magnetic stimulation of human area V5/MT. *Proc R Soc Lond B Biol Sci* 249: 173–178, 1992.
- Brighina F, Piazza A, Daniele O, Fierro B.** Modulation of visual cortical excitability in migraine with aura: effects of 1 Hz repetitive transcranial magnetic stimulation. *Exp Brain Res* 145: 177–181, 2002.
- Brighina F, Vitello G, Piazza A, Scalia S, Giglia G, Daniele O, Pascual-Leone A.** Modulatory effects of low- and high-frequency repetitive transcranial magnetic stimulation on visual cortex of healthy subjects undergoing light deprivation. *J Physiol* 565: 659–665, 2005.
- Campana G, Cowey A, Walsh V.** Priming of motion perception and area V5/MT: a test of perceptual memory. *Cereb Cortex* 12: 663–669, 2002.
- Campana G, Cowey A, Walsh V.** Visual area V5/MT remembers “what” but not “where.” *Cereb Cortex* 16: 1766–1770, 2006.
- Cowey A.** The Ferrier Lecture 2004 what can transcranial magnetic stimulation tell us about how the brain works? *Philos Trans R Soc Lond B Biol Sci* 360: 1185–1205, 2005.
- Cummings JL.** The neuroanatomy of depression. *J Clin Psychol* 54: 14–20, 1993.
- Gerschlagler W, Siebner HR, Rothwell JC.** Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. *Neurology* 57: 449–455, 2001.
- Green DM, Swets JA.** *Signal Detection Theory and Psychophysics*. New York: John Wiley, 1966.
- Grossman ED, Battelli L, Pascual-Leone A.** Repetitive TMS over posterior STS disrupts perception of biological motion. *Vision Res* 45: 2847–2853, 2005.
- Harris JA, Clifford CWG, Miniussi C.** The functional effect of transcranial magnetic stimulation: signal suppression or neural noise generation? *J Cogn Neurosci* 20: 734–740, 2008.
- Hilgetag CC, Theoret H, Pascual-Leone A.** Enhanced visual spatial attention ipsilateral to rTMS-induced “virtual lesions” of human parietal cortex. *Nat Neurosci* 4: 953–957, 2001.
- Hotson JR, Anand S.** The selectivity and timing of motion processing in human temporo-parieto-occipital and occipital cortex: a transcranial magnetic stimulation study. *Neuropsychologia* 37: 169–179, 1999.
- Kobayashi M, Pascual-Leone A.** Transcranial magnetic stimulation in neurology. *Lancet Neurol* 2: 145–156, 2003.
- Lang N, Siebner HR, Ernst D, Nitsche MA, Paulus W, Lemon RN, Rothwell JC.** Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. *Biol Psychiatry* 56: 634–639, 2004.
- Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A.** Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clin Neurophysiol* 111: 800–805, 2000.
- Matthews N, Luber B, Qian N, Lisanby SH.** Transcranial magnetic stimulation differentially affects speed and direction judgments. *Exp Brain Res* 140: 397–406, 2001.
- Mazzocchio R, Rothwell JC, Day BL, Thompson PD.** Effect of tonic voluntary activity on the excitability of human motor cortex. *J Physiol* 553: 665–679, 1994.
- Moliadze V, Zhao Y, Eysel U, Funke K.** Effect of transcranial magnetic stimulation on single-unit activity in the cat primary visual cortex. *J Physiol* 553: 665–679, 2003.
- Muggleton NG, Postma P, Moutsopoulou K, Nimmo-Smith I, Marcel A, Walsh V.** TMS over right posterior parietal cortex induces neglect in a scene-based frame of reference. *Neuropsychologia* 44: 1222–1229, 2006.
- O’Shea J, Johansen-Berg H, Trif D, Göbel S, Rushworth MF.** Functionally specific reorganization in human premotor cortex. *Neuron* 54: 479–490, 2007.
- O’Shea J, Muggleton NG, Cowey A, Walsh V.** Timing of target discrimination in human frontal eye fields. *J Cogn Neurosci* 16: 1060–1067, 2004.
- Pascual-Leone A, Walsh V.** Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science* 292: 510–512, 2001.
- Pitcher D, Walsh V, Yovel G, Duchaine B.** TMS evidence for the involvement of the right occipital face area in early face processing. *Curr Biol* doi:10.1016/j.cub.2007.07.063, 2007.
- Raiguel SE, Lagae L, Gulyas B, Orban GA.** Response latencies of visual cells in macaque areas V1, V2, and V5. *Brain Res* 493: 155–159, 1989.
- Rauschecker AM, Bestmann S, Walsh V, Thilo KV.** Phosphene threshold as a function of contrast of external visual stimuli. *Exp Brain Res* 157: 124–127, 2004.
- Ridding MC, Rothwell JC.** Is there a future of therapeutic use of transcranial magnetic stimulation? *Nat Rev Neurosci* 8: 559–567, 2007.

- Sack AT, Kohler A, Bestmann S, Linden DE, Dechent P, Goebel R, Baudewig J.** Imaging the brain activity changes underlying impaired visuo-spatial judgments: simultaneous fMRI, TMS, and behavioral studies. *Cereb Cortex* 17: 2841–2852, 2007.
- Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, Rothwell JC.** Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J Neurosci* 24: 3379–3385, 2004.
- Silvanto J, Lavie N, Walsh V.** Double dissociation of V1 and V5/MT activity in visual awareness. *Cereb Cortex* 15: 1736–1741, 2005.
- Silvanto J, Muggleton NG.** New light through old windows: moving beyond the virtual lesion approach to transcranial magnetic stimulation. *Neuroimage* 39: 549–552, 2008a.
- Silvanto J, Muggleton NG.** A novel approach for enhancing the functional specificity of TMS: revealing the properties of distinct neural populations within the stimulated region. *Clin Neurophysiol* 119: 724–726, 2008b.
- Silvanto J, Muggleton NG, Cowey A, Walsh V.** Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation. *Eur J Neurosci* 25: 1874–1881, 2007a.
- Silvanto J, Muggleton NG, Cowey A, Walsh V.** Neural activation state determines behavioral susceptibility to transcranial magnetic stimulation. *Eur J Neurosci* 26: 523–528, 2007b.
- Stewart L, Battelli L, Walsh V, Cowey A.** Motion perception and perceptual learning studied by magnetic stimulation. *Electroenceph Clin Neurophysiol Suppl* 51: 334–350, 1999.
- Tyrell RA, Owens DA.** A rapid technique to assess the resting states of the eye and other threshold phenomena: the modified binary search (MOBS). *Behav Res Methods Instrum Comput* 20: 137–141, 1988.
- Valentin A, Arunachalam R, Mesquita-Rodrigues A, Garcia Seoane JJ, Richardson MP, Mills KR, Alarcon G.** Late EEG responses triggered by transcranial magnetic stimulation (TMS) in the evaluation of focal epilepsy (Epub ahead of print). *Epilepsia* 2007.
- Valero-Cabré A, Payne BR, Pascual-Leone A.** Opposite impact on 14C-2-deoxyglucose brain metabolism following patterns of high and low frequency repetitive transcranial magnetic stimulation in the posterior parietal cortex. *Exp Brain Res* 176: 603–615, 2007.
- Valero-Cabre A, Payne BR, Rushmore J, Lomber SG, Pascual-Leone A.** Impact of repetitive transcranial magnetic stimulation of the parietal cortex on metabolic brain activity: a 14C-2DG tracing study in the cat. *Exp Brain Res* 163: 1–12, 2006.
- Wagner T, Valero-Cabre T, Pascual-Leone A.** Noninvasive human brain stimulation. *Annu Rev Biomed Eng* 9: 527–565, 2007.
- Walsh V, Pascual-Leone A.** *Transcranial Magnetic Stimulation: A Neurochronometrics of Mind* (1st ed.). Boston, MA: MIT Press, 2003.