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The effect of TMS on visual motion sensitivity: an increase in neural noise or a decrease in signal strength?

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The underlying mechanisms of action of transcranial magnetic stimulation (TMS) are still a matter of debate. TMS may impair a subject’s performance by increasing neural noise, suppressing the neural signal, or both. Here, we delivered a single pulse of TMS (spTMS) to V5/MT during a motion direction discrimination task while concurrently manipulating the level of noise in the motion stimulus. Our results indicate that spTMS essentially acts by suppressing the strength of the relevant visual signal. We suggest that TMS may induce a pattern of neural activity that complements the ongoing activation elicited by the sensory signal in a manner that partially impoverishes that signal.

V5/MT; single pulse of transcranial magnetic stimulation

IN BEHAVIORAL STUDIES THAT employ transcranial magnetic stimulation (TMS), the most often analyzed dependent variables are accuracy and reaction time (for a review, see Sandrini et al. 2011). Both of these variables are affected by the signal-to-noise ratio: higher ratios are associated with greater accuracy and shorter reaction times (cf. the linking hypothesis: Teller 1984). TMS has an effect on this ratio (Harris et al. 2008; Rauschecker et al. 2004; Sack et al. 2006; Silvanto et al. 2008) by reducing the strength of the signal (Harris et al. 2008), increasing the neural noise (Ruzzoli et al. 2010), or both.

The “virtual lesion” hypothesis, by analogy with animal and human neuropsychological studies, states that TMS-induced effects are interpretable as a temporary and reversible halt of the functionality of the stimulated area as a consequence of the discharge of magnetic pulses (Pascual-Leone et al. 1999; Walsh and Cowey 1998). Although the virtual lesion is the most common theoretical framework used to interpret the behavioral effects of TMS, it does not provide a clear explanation of the underlying neural mechanisms (Miniussi et al. 2010). Recent human (Harris et al. 2008; Ruzzoli et al. 2010; Silvanto et al. 2008) and animal (Allen et al. 2007; Moliadze et al. 2003; Pasley et al. 2009) studies have provided important clues to some of the mechanisms underlying the effects of TMS. Studies investigating the effects of TMS on stimulus-evoked activity in visual cortex of anesthetized cats (Allen et al. 2007; Moliadze et al. 2003; Pasley et al. 2009) have suggested that TMS acts by reducing the evoked neural activity (Allen et al. 2007). The effect depends on the TMS parameters (Allen et al. 2007; Pasley et al. 2009) as well as on the timing of stimulation (Moliadze et al. 2003), therefore yielding a complex pattern of results.

Harris and colleagues (2008) used an added noise paradigm (Pelli and Farell 1999) to compare the functional effects of TMS on signal strength vs. noise. They applied a single pulse of TMS (spTMS) to the occipital pole while subjects discriminated the orientation of sinusoidal luminance gratings to which were added varying levels of spatial white noise. The orientation detection thresholds were established using an adaptive staircase procedure. The primary aim of that experiment was to ascertain the impact of TMS on the linear function between the square of the detection thresholds (contrast energy) and the square of the amount of noise added to the stimulus [noise variance ($\sigma^2$)]. Harris et al. (2008) found that the slope of the psychometric function increased more than double when spTMS was applied to visual cortex, compared with a control condition, but there was no evidence for a change in the x-intercept of the linear function. These observations were interpreted as showing that spTMS reduced the effective signal strength but did not add statistical noise to the sensory information on which the perceptual judgment was based (Harris et al. 2008). The authors concluded that spTMS essentially acts by suppressing the strength of the signal by interrupting stimulus processing.

The conclusions reached by Harris and coworkers (2008) contrast with those of a recent study by Ruzzoli and colleagues (2010). In the latter study, they used a repetitive TMS (rTMS) protocol to stimulate the motion-sensitive area V5/MT in the extrastriate visual cortex while subjects judged the direction of coherent motion in a random dot kinematogram (RDK). The coherence of dots was systematically varied across five levels corresponding to the percent coherence necessary for the subjects to reach 50, 55, 70, 75, and 90% accuracy on a two-alternative forced-choice (2AFC) discrimination task. Ruzzoli et al. (2010) found that the rTMS flattened the psychometric function, which related motion coherence to accuracy, and interpreted this result as suggesting that rTMS introduces random neural noise in the stimulated area instead of a reduction of the strength of the signal.
In comparing the two studies described above (Harris et al. 2008; Ruzzoli et al. 2010), one should bear in mind that they involved different TMS protocols (spTMS vs. rTMS) and different cortical areas (V1 vs. V5/MT). Furthermore, in the study by Ruzzoli et al. (2010), signal and noise were concurrently manipulated through the levels of motion coherence, since the total number of dots was fixed, and thus increasing the number of coherently moving dots meant reducing the number of randomly moving dots. A more advantageous method to tease apart possible changes in signal strength from changes in noise is to vary them independently (Pelli and Farell 1999). A convenient way to do this is to measure the subjects’ perceptual thresholds, as the strength of signal required to detect or discriminate the stimulus while independently varying the level of noise added to the stimulus (e.g., Harris et al. 2008). That is, the added noise paradigm (Pelli and Farell 1999) provides the opportunity to make independent estimates of the change in slope and intercept of the psychometric function across different TMS conditions.

In light of these issues, the present experiment was conducted to define better the mechanisms of action of TMS from a psychophysical point of view. The psychophysical approach was comparable with that used by Harris et al. (2008) but was applied here to investigate the effects of spTMS to V5/MT during a motion direction discrimination task using an RDK stimulus. Rather than keeping the number of dots constant while varying the proportion of coherence, the present experiment independently varied the number of random and coherent dots in the display, therefore ensuring equal levels of noise in each display. We chose four levels of noise, implemented as different numbers of randomly moving dots, to which we added coherently moving dots. The number of coherently dots varied according to an adaptive staircase procedure (Kontsevich and Tyler 1999) used to identify the subjects’ motion discrimination thresholds. These thresholds were defined as the number of coherent dots that needed to be added to the random dot display to discriminate the direction of coherent motion. According to signal detection theory (Green and Swets 1966), there is a linear relationship between the square of a psychophysical threshold ($T^2$) and $\sigma^2$, a relationship that was confirmed empirically in the study by Harris and colleagues (2008). This linear relationship is convenient because it provides the basis for three distinct predictions for testing the effects of TMS on sensory processing. First, if TMS introduces random neural noise in the target area (V5/MT), this should be evident as a parallel shift in the linear relationship between $\sigma^2$ and $T^2$ (revealed by a decrement of the $y$-intercept of the line) compared with a control condition. This prediction derives from the argument that TMS, as an independent source of (external) noise, will add a fixed increment to the total $\sigma^2$ (because variances are additive when independent sources of noise are combined). Such a fixed increment will be evident as a parallel shift of the line. A different prediction is made if TMS acts by selectively reducing the signal strength. In this case, TMS will interact multiplicatively with the level of stimulus noise, resulting in an increase of the slope of the linear function. For example, if TMS halves the strength of the signal, this will double the slope of the line relating $T^2$ to $\sigma^2$ because, at each level of noise, twice as much signal must be added to the stimulus to reach the same discrimination accuracy. Finally, it is also possible that TMS will act on both parameters ($x$-intercept and slope), inducing a leftward shift and an increase in slope. It is important to note that in all these cases, the $y$-intercept (the threshold when no noise has been added to the stimulus) will increase, which is consistent with the general observation that TMS interferes with perceptual sensitivity, such as has been shown for motion direction discriminations when TMS is applied over V5/MT (Anand et al. 1998; Beckers and Homberg 1992; Beckers and Zeki 1995; Hotson et al. 1994; Hotson and Anand 1999; Matthews et al. 2001; Sack et al. 2006).

Materials and Methods

Subjects. Five healthy right-handed subjects (aged 22–40 yr, 3 males), with no contraindications to TMS, participated in the experiment as volunteers. Their visual acuity was normal or corrected to normal. Two subjects were authors, M. Ruzzoli and J. A. Harris, and the other three were naïve to the aim of the experiment. All subjects gave informed consent, and the experimental protocol was approved by the Human Research Ethics Committee at the University of Sydney.

Stimuli. The stimuli were presented on a 19-in. cathode ray tube (CRT) monitor (BENQ P992) with a refresh rate set at 75 Hz and a midgray uniform background (luminance = 77 cd/m$^2$). The stimulus was an RDK consisting of black and white dots (dot-size = 1 pixel) in a virtual circle (5° in diameter) positioned in the bottom-right quadrant of the monitor 15° from a central fixation square. The total duration of the stimulus was 146 ms (11 frames), but only the last 40 ms contained motion. Perceptually, a stationary dot display appeared for 106 ms (8 frames), followed by 3 frames of motion. The static display was presented for the 1st 106 ms to reduce the amount of forward masking caused by the abrupt onset of the stimulus. We chose to present the stimulus in the lower right quadrant of the visual field because all of subjects reported TMS-induced phosphenes in that location. The dots moved at the speed of 6°/s. Within each block, the number of randomly moving dots was kept constant. We chose 4 levels of noise (10, 58, 82, and 100 randomly moving dots) that were approximately equidistant when squared, consistent with our aim to plot the linear relationship between the $T^2$ and $\sigma^2$ (Green and Swets 1966; Harris et al. 2008). The number of coherently moving dots was varied according to an adaptive staircase procedure (Kontsevich and Tyler 1999) to measure the participants’ motion direction discrimination threshold. The threshold was set to yield an accuracy of 80.3%, which corresponded to the position parameter of a Weibull function fitted to the proportion of correct responses with a lapse rate of 4%. The direction of coherent motion was either leftward or rightward.

Procedure. The subjects were seated in a dark room with their head supported by a chin rest and forehead rest facing the computer monitor at a distance of 57 cm. A small, white square was presented as a fixation point in the center of the screen, and subjects were asked to maintain fixation throughout the experiment. After 500 ms, the RDK was presented in the right visual field. The subjects performed a 2AFC task indicating the direction of coherent motion (left or right) by pressing either left or right “Shift” keys, respectively. Motion direction threshold was estimated from 30 trials through an adaptive staircase procedure. For each TMS condition (V5/MT and Cz), we collected 3 threshold measurements at each level of noise during 1 experimental session. There was a total of 3 sessions run on 3 consecutive days. Thus there were 9 separate measurements of the threshold in each of the 8 conditions (2 TMS conditions by 4 levels of noise) for every subject.

fMRI procedure. The TMS coil was positioned with respect to the cortical region of interest (left V5/MT) using a SofTaxic Optic neuronavigation system (E.M.S., Bologna, Italy) guided by functional magnetic resonance imaging (fMRI) of V5/MT. fMRI data were acquired using a T2*-sensitive, field-echo planar imaging (FEPI) pulse sequence with echo time (TE) of 32 ms, time to repetition (TR) of 3,000 ms, flip angle 90°, field of view 192 × 70.5 × 192 mm, effective in-plane resolution 1.5 × 1.5 mm, and slice thickness 1.5

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mm. Forty-seven slices were collected in an interleaved, ascending order, in a coronal plane tilted such that the scan covered the whole of the occipital lobe and the posterior part of the parietal and temporal lobes. Using SPM5, all functional data were preprocessed to correct for slice time and head motion before alignment to the structural data. Data from functional scans were aligned to a whole head anatomic scan acquired in the same session, using normalized mutual information-based coregistration. Area V5/MT was defined on the basis of scans in which blocks of low-contrast static and moving dots were interleaved with fixation-only blocks. In SPM5, we specified a general linear model of these data and defined V5/MT in each hemisphere as a lateral cluster of voxels that responded more to moving than to static dots.

TMS protocol. TMS was applied using a Magstim Rapid² magnetic stimulator and a figure-of-8 coil (70-mm diameter; Magstim, Whitland, United Kingdom). During the experiment, the stimulating coil was fixed by means of a mechanical support that consisted of an articulated arm (Manfrotto Magic Arm with 2 clamps). At the same time, the position of the coil with respect to the participant’s head was monitored in real-time using the SoTaxic Optic neuronavigation system, which provides an integration of spatial data related to the stimulation coil and the brain anatomy of the subject. The system allows the operator to localize the cerebral area beneath the point of maximum intensity of the coil (focus) and therefore to reposition the coil on the subject’s head with an error tolerance. After each block, subjects were invited to readjust the relative position of the coil by tilting their head gently in small increments while monitoring the coil position on a computer screen. This procedure maintained the coil position within 2 mm of the target brain area. To stimulate V5/MT, we placed the junction of the 2 coil wings above the target area defined by individual fMRI activation. The coil was oriented perpendicular to the scalp midline with the handle pointing leftward. After the coil was set in place, spTMS was delivered to ensure that the single pulses evoked reliable and localized phosphenes, which, in at least 2 subjects, appeared to move. The individual phosphenes thresholds were assessed using an adaptive staircase procedure in which the subjects performed a yes/no task, reporting after each TMS pulse the presence of a phosphenone (A. Abrahamyan, C. W. Clifford, M. Ruzzoli, D. Phillips, E. Arabzadeh, and J. A. Harris, unpublished observations). The threshold identified by this procedure was equivalent to a detection accuracy of 60%. The phosphenes threshold was measured twice, and the final threshold was the average of the 2 measurements. The mean phosphenes threshold across subjects was 55% (±3.26%) of the output of the stimulator. Individual phosphenes thresholds are provided in Table 1. None of the subjects reported perceiving phosphenes during the motion discrimination task.

During the experimental sessions, spTMS was delivered on each trial 133 ms (10 frames) after the onset of motion in the stimulus with an intensity of 20% above the phosphenes threshold. This timing was based on the results from previous studies (Laycock et al. 2007; Sack et al. 2006) and our own pilot testing.

The control condition involved active stimulation over Cz, a location that corresponds to a brain area that is supposedly not involved in visual processing. The order of the two locations of TMS application, i.e., V5/MT and Cz stimulation, and the order of the levels of noise were randomized across subjects and across daily sessions within the same subject.

Statistical analysis. For each subject, we collected at least nine threshold estimates for each level of noise and TMS condition. The T2 (the square of the number of coherent dots) was plotted as a function of the σ2 (the square of the number of random dots) separately for both TMS conditions. We performed a linear fit for each subject and TMS condition to estimate the slope and x-intercept across the levels of noise. A Wilcoxon signed-rank test was used to determine statistical differences (P < 0.05) in the slope and intercept values between TMS conditions.
The initial linear fit was performed allowing the two parameters (slope and intercept) to vary freely. To assess whether the two-parameter model was necessary to explain the data, we compared it against the one-parameter models, one of which fixed the slope and allowed the intercept to vary, and the other fixed the intercept and allowed the slope to vary. If the two-parameter model provides a significantly better linear fit to the data than both of the one-parameter models, we can conclude that the two-parameter model is superior. On the other hand, if either one-parameter model provides as good a fit to the data, that model should be preferred (Wichmann and Hill 2001).

RESULTS

The results are presented in Fig. 1, plotting \( T^2 \) against \( \sigma^2 \), both expressed in terms of number of dots, and in Fig. 2. As expected, the relationship between \( T^2 \) and \( \sigma^2 \) is well-described by a linear function in both TMS conditions. Stimulation of V5/MT led to an increase in the number of coherent dots necessary for subjects to perceive correctly the direction of motion. All subjects clearly showed an increase in the slope of the function for the V5/MT TMS condition compared with the Cz TMS condition (Fig. 2A). Only one subject (SM) showed a decrease (leftward shift) in the \( x \)-intercept due to the V5/MT stimulation (Fig. 2B). The statistical comparisons between the two TMS conditions following the two-parameter (slope and \( x \)-intercept) model revealed that the difference in the slope of the functions is significant (Wilcoxon signed-rank test, \( z = -2.023, P = 0.04 \)).

We investigated further the difference between the two TMS conditions in their linear relation between \( T^2 \) and \( \sigma^2 \). Initially, we fitted a two-parameter model to the data from both TMS conditions; this model fitted separate lines to each condition with independent slopes and intercepts (as described above). The fit of this two-parameter model was then compared with a one-parameter model that fitted lines to the two conditions that had independent slopes but a common intercept (or vice versa). Fixing the \( x \)-intercept in this model did not reduce the goodness-of-fit of the lines in each TMS condition compared with the two-parameter model. This confirms that there was no reliable evidence for a difference in the \( x \)-intercept between the two TMS conditions. By contrast, a different one-parameter model that fixed the slope of the two lines but allowed their intercepts to vary independently, provided a worse fit in all subjects [V5 TMS: \( F_{(2,8)} = 31.41; P < 0.01 \); Cz TMS: \( F_{(2,8)} = 10.61; P < 0.01 \)]. This confirms that there is a difference in the slopes of the lines between the two TMS conditions. Table 1 presents individual values associated with the linear fits in both TMS conditions and model comparisons. As is evident from Table 1 and from individual subjects’ data (Figs. 1 and 2), there is large variability between subjects in both TMS conditions. This variability might be related to the TMS intensity used. As described above, TMS intensity was set 20% above the individual phosphene threshold, which itself differed considerably between subjects. Some evidence that the effect was related to stimulation intensity comes from the observation that the phosphene threshold and slope were negatively correlated in both V5/MT (\( r^2 = -0.73 \)) and Cz (\( r^2 = -0.75 \)) TMS conditions, although neither of these correlations was statistically significant.

![Fig. 1. Data of single subjects [SM, DM, M. Ruzzoli (MR), J. A. Harris (JH), and JC] for 2 transcranial magnetic stimulation (TMS) conditions [V5 and vertex (Cz)]. Squares are associated with Cz data points, and solid lines represent fittings to Cz TMS data. Triangles indicate V5 TMS data points, and dotted lines are V5 TMS data fitting. Error bars represent the standard error of the mean. Please note that, since the graphs are related to individual visual thresholds, the y-axis scale is different between subjects. T\(^2\), psychophysical threshold.](https://www.jn.org)
increase in slope comparing the V5/MT and Cz conditions. Only one subject showed evidence of a leftward shift in the psychometric function. No significant correlations were found between individual thresholds and individual visual motion threshold, which might otherwise explain the between-subjects variability. Therefore, the x-intercept shift shown by subject SM is likely to be due to random variability. Most important is that, overall, our results show that spTMS over V5/MT interrupts motion signal processing by selectively suppressing the strength of the relevant visual signal.

These results are consistent with those reported previously by Harris and colleagues (2008) using the same rationale as in the present experiment. Therefore, a reasonable conclusion is that high-intensity spTMS delivered to the visual cortex causes a suppression of the relevant sensory signal. This effect holds across different types of visual tasks (discrimination of grating orientation or direction of motion) and two different cortical areas (occipital pole and V5/MT).

Since TMS essentially introduces activity into the stimulated area by means of rapid changes in the magnetic field (Ruzzoli et al. 2003), how does TMS act to decrease the strength of the signal? One possibility is that TMS momentarily disables neuronal function leading to a loss of whatever information was coded by the activity of the affected neurons. Alternatively, the effect of TMS on neuronal activity may not be random addition of noise. For example, there is evidence suggesting that the effect of TMS on neuronal activity may not be random addition of noise. For example, there is evidence suggesting that the effect of TMS on neuronal activity may not be random addition of noise.

A different conclusion on the effect of TMS was formulated by Ruzzoli et al. (2010). In their study, the behavioral consequences of rTMS discharged to V5/MT during a motion-direction discrimination task were consistent with the hypothesis that rTMS induces random neural noise. The main difference between Ruzzoli et al. (2010) and the present study is the psychophysical approach. Ruzzoli et al. (2010) concurrently varied coherent motion (signal) and random motion (noise). By plotting the proportion of rightward choice against the motion coherence level, a shallower slope in the psychometric function is consistent with greater variability (increment of random noise; e.g., Parker and Newsome 1998). However, in that approach, it is difficult to disentangle changes in signal strength from noise because the two factors are varied concurrently. The approach used in the present experiment allowed us to clarify the effect of TMS on observer’s performance by independently manipulating signal strength and noise by means of the added-noise paradigm (Pelli and Farell 1999).

Fig. 2. Single subjects’ changes in slope (A) and x-intercept (B). A: individual slope change is represented as ratio between V5/MT TMS and vertex TMS (Cz). The thick line represents no change. All subjects showed an increment in slope after V5/MT TMS. B: the histograms represent the difference between x-intercepts after vertex TMS (Cz) and V5/MT TMS for each subject. Only 1 subject (SM) showed the leftward shift of the x-intercept. In DM, MR, and JH, the x-intercept slightly shifted to the right. JC had a big rightward shift of the x-intercept.

The presence of a leftward shift of the x-intercept in one subject (SM) could be taken as evidence that TMS added noise in that subject. However, in our sample of subjects, another subject (JC) showed the opposite pattern of results (a rightward shift of the x-intercept), and the other three subjects had negligible shifts of intercept. Therefore, we believe that the most likely interpretation of the full set of data is that TMS had no effect on the x-intercept and that any shift that was observed in individual subjects was due to measurement variability.

DISCUSSION

The present study investigated the functional effects of spTMS delivered to area V5/MT on a motion direction discrimination task. By plotting T2 against σ2 of the motion display (RDK), it was possible to test the validity of three hypotheses. First, if TMS acts as an external source of noise to sensory information, we would predict that TMS delivered to V5/MT should produce a parallel leftward shift (i.e., a more negative x-intercept) of the line relating T2 to σ2. Alternatively, if TMS acts by selectively suppressing the strength of the neural signal, we would predict a multiplicative interaction between TMS and noise in the motion display yielding an increase of the slope of the line relating T2 to σ2. The third possibility is that TMS affects both elements of the signal-to-noise ratio, suppressing the relevant signal and introducing random noise in the stimulated brain area. The results presented here are in support of the second hypothesis: TMS to V5/MT increased the slope of the function in all five subjects, and the size of this effect varied between a 50 and 170% increase in slope comparing the V5/MT and Cz conditions. Only one subject showed evidence of a leftward shift in the psychometric function. No significant correlations were found between individual thresholds and individual visual motion threshold, which might otherwise explain the between-subjects variability. Therefore, the x-intercept shift shown by subject SM is likely to be due to random variability. Most important is that, overall, our results show that spTMS over V5/MT interrupts motion signal processing by selectively suppressing the strength of the relevant visual signal.
population of neurons, mostly irrelevant for the task execution, through temporal summation effects and that the random noise results from a nonlinear interaction with the ongoing neural activity. Thus from a physiological point of view, the effect of a series of pulses might be different from the effects of a single pulse. Repetitive stimulation is characterized by a train of pulses discharged in a brief time based on frequency (e.g., 15 Hz in Ruzzoli et al. 2010). So, although spTMS leads to signal suppression, it is plausible that rTMS adds neural noise in the stimulated area. If we consider that spTMS acts through a saturation of neurons activated by the task, a rapid repetition has more chance to activate also neighboring neurons irrelevant for task execution.

This possibility seems to be corroborated by recent findings in animal models (Allen et al. 2007; Moliadze et al. 2003; Pasley et al. 2009). Specifically, considering the effect of TMS on spontaneous activity, the main result is an increment of neural activation when there is no information to be processed. Observable TMS effects essentially consist of adding generalized electrical activity in the stimulated area. By contrast, the effects of the same TMS protocol (brief train of TMS) induced an opposite pattern of result on the visual evoked activity in anesthetized cats (Allen et al. 2007; Pasley et al. 2009). Furthermore, one should consider that when adopting an rTMS paradigm, the frequency of stimulation should be taken into account. There is evidence that the oscillation of neural activity is affected by TMS (Thut and Miniussi 2009), thus it is possible that rTMS acts on the neural synchronization between and within cortical areas involved in the task execution. In Allen et al. (2007) and Pasley et al. (2009), one can find direct evidence that brief trains of TMS alter the temporal structure of neural activity. It should be noted that, even though TMS seems to introduce neural activity in the stimulated neurons, the TMS-induced effect may not be random. That is, the activity induced by TMS may not be independent of the stimulus-induced neural activity (Silvanto et al. 2008), in which case the effect of TMS is not statistically pure noise.

Based on the present data, we conclude that spTMS, applied to different cortical visual areas (V1 and V5/MT) and using area-specific tasks, exerts its effects by suppressing the strength of the representation of the stimulus encoded in a neural population.

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DISCLOSURES

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