The Functional Effect of Transcranial Magnetic Stimulation: Signal Suppression or Neural Noise Generation?

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Abstract

■ Transcranial magnetic stimulation (TMS) is a popular tool for mapping perceptual and cognitive processes in the human brain. It uses a magnetic field to stimulate the brain, modifying ongoing activity in neural tissue under the stimulating coil, producing an effect that has been likened to a "virtual lesion." However, research into the functional basis of this effect, essential for the interpretation of findings, lags behind its application. Acutely, TMS may disable neuronal function, thereby interrupting ongoing neural processes. Alternatively, the effects of TMS have been attributed to an injection of "neural noise," consistent with its immediate and effectively random depolarization of neurons. Here we apply an added-noise paradigm to test these alternatives. We delivered TMS to the visual cortex and measured its effect on a simple visual discrimination task, while concurrently manipulating the level of image noise in the visual stimulus itself. TMS increased thresholds overall; and increasing the amount of image noise systematically increased discrimination thresholds. However, these two effects were not independent. Rather, TMS interacted multiplicatively with the image noise, consistent with a reduction in the strength of the visual signal. Indeed, in this paradigm, there was no evidence that TMS independently added noise to the visual process. Thus, our findings indicate that the "virtual lesion" produced by TMS can take the form of a loss of signal strength which may reflect a momentary interruption to ongoing neural processing. ■

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a technique that uses a magnetic field to produce indirect electrical stimulation of the brain (Barker, Jalinous, & Freeston, 1985). The induced stimulation modifies ongoing activity in the neural tissue under the stimulating coil, with the effect that TMS can impair performance on a wide range of perceptual and cognitive tasks (Cowey, 2005; Hallett, 2000; Pascual-Leone, Walsh, & Rothwell, 2000; Walsh & Cowey, 2000). As such, TMS has often been described as creating a "virtual lesion" (Hallett, 2000; Pascual-Leone et al., 2000), but this description can be interpreted in different ways (Walsh & Cowey, 2000). One way to describe the functional impact of TMS is that it temporarily disables neuronal function, thereby interrupting processing of the information (signal) carried by the activity of the afflicted neurons. Thus, for example, if a target area accumulates information about a sensory event, then TMS would abort that process and effectively reduce the net strength of the perceptual signal. An alternative view is that TMS introduces random noise in neural processing by inducing neuronal activity that is uncorrelated with the ongoing task-related activity of those neurons. According to this account, the signal is not reduced but is masked by an increase in background noise. In either case, however, the behavioral effect will be the same—a decline in performance.

Available evidence concerning the physiological response to TMS is equivocal. Moliadze, Zhao, Eysel, and Funke (2003) recorded single-unit neuronal activity in the cat visual cortex during presentations of single pulses of TMS. They observed a pattern of excitation and inhibition that lasted up to 500 msec after the pulse, as well as a depression of spontaneous activity lasting one or more seconds. Conceptually, the induced pattern of discharge and suppression could erase whatever information was carried by the precise firing pattern of the afflicted neurons at the time of the TMS. Alternatively, the random activity induced by the TMS could simply sum with the neurons' ongoing firing pattern. In other words, the observed impact of TMS on neuronal activity could be interpreted as a loss of signal strength or simply the addition of noise to signal processing.

The present study seeks to identify the functional impact of TMS, and in particular, to test whether TMS adds noise to signal processing or reduces signal strength. We adopt a formal statistical definition of noise that allows us to describe how signal information and noise interact

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and therefore derive distinct testable predictions about the effect of TMS. We measured the effect of TMS delivered to the visual cortex of human subjects while they performed a simple visual discrimination task. We concurrently manipulated the level of image noise in the visual stimulus itself (Figure 1). Threshold contrast power, T^2, is a direct linear function of the variance of the noise added to the image (Green & Swets, 1966; see Analysis section under the Methods section below for a detailed description of the relationship between T^2 and image noise). Therefore, if TMS adds further noise, this will produce an overall increase in T^2, observable as a leftward shift in the line relating T^2 to the variance of image noise. Indeed, if TMS noise and image noise have equivalent effects on signal processing, then TMS should cause a fixed increase in T^2, and thus, produce a parallel shift in the relation between T^2 and image noise (as illustrated in Figure 2A). However, the shift may not be parallel if the response of the visual system to the image (including noise present in the image) is subject to nonlinear gain control (e.g., Heeger, 1993) operating "upstream" from the site of TMS. A gain control process would moderate the response of the visual system as the overall contrast of the stimulus increases, keeping the gain in the system constant, and therefore, increasing the amount of image noise would cause a proportional reduction in signal strength. If TMS affects neurons "downstream" of this gain control, the amount of noise added by TMS would increase relative to the signal strength as the image noise increased, even though the amount of random neuronal activity induced by TMS would be constant. As a result, there would be an interaction between the effects of TMS and image noise (see Dao, Lu, & Dosher, 2006), such that TMS would increase the slope of the line relating to T^2 to the variance of image noise, as well as shifting that line to the left (Figure 2B).

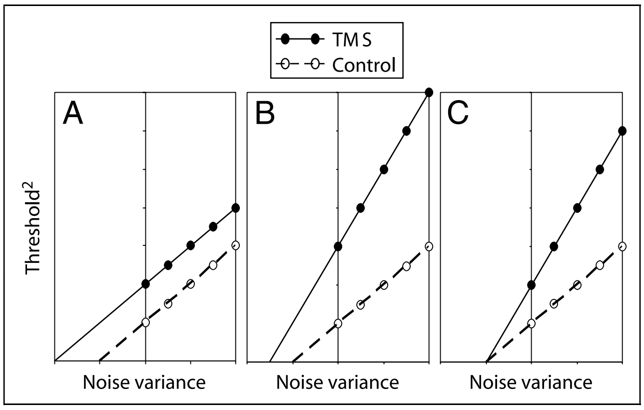
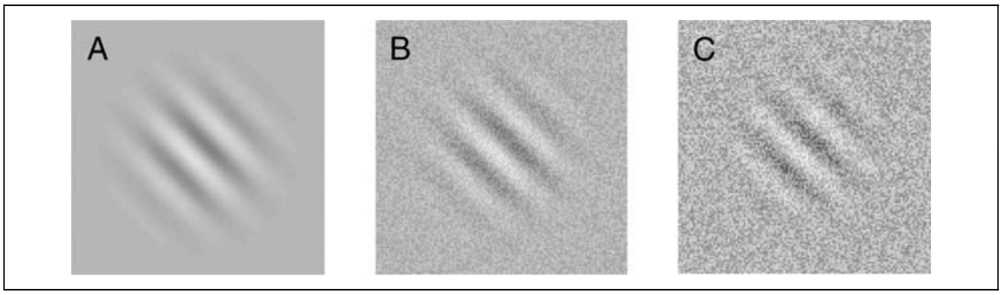


Figure 2. Graphical illustrations of three hypothesized effects of TMS on squared detection thresholds as plotted against variance of image noise. (A) shows a parallel leftward shift induced by the simple addition of noise from TMS; (B) shows a leftward shift and increase in slope created by TMS-induced noise added downstream of a gain control process operating on the signal and image noise; (C) shows an increase in slope (without leftward shift) created by a TMS-induced decrease in signal strength (relative to noise). Note that an increase in threshold indicates a decrease in sensitivity, and therefore lower threshold^2 values reflect better performance.

Alternatively, TMS may reduce the efficiency of visual processing without adding noise, and therefore, without inducing a leftward shift in the line relating T^2 to image noise. This could occur if TMS interrupts visual processing, thereby reducing the effective strength of the visual signal and increasing the slope of the line relating T^2 to image noise (Figure 2C; see Pelli & Farell, 1999). For example, with a spatially periodic pattern, such as the sine wave grating we have used here, information about the visual image requires the integration of activity across a distributed population of cortical neurons. In this case, the total signal strength would increase approximately linearly with an increase in the number of neurons responding to the stimulus. In contrast, uncorrelated noise (both internally generated neural noise and image noise) would increase with the square root of the number of neurons because the variances of uncorrelated sources of noise combine additively, and thus, the standard deviation increases as the square root of the summed variances. Therefore, if TMS interrupted ongoing activity in half of these cortical neurons, this would reduce the strength of the signal representing the

Figure 1. (A) The target stimulus was presented on a mid-gray background in the lower right visual field (at the perceived location of phosphenes induced beforehand by TMS pulses), and the contrast was varied to measure the participant's detection threshold. (B, C) Image noise was added by superimposing spatial white noise, drawn from a uniform distribution, onto the grating. These examples show noise variances of 0.0033 (B) and 0.0133 (C).



grating by 50% but reduce the uncorrelated noise by only 30%. That is, the efficiency of the visual system would be reduced. It should be noted that the degree of reduction would depend on the noise correlation between neurons. If noise is positively correlated between neurons, this will increase the sum of the variance across those neurons, and thus, a TMS-induced interruption to activity will have a smaller impact on efficiency. Conversely, if noise is negatively correlated between neurons, this will reduce the summation of their variances, and so increase the impact of TMS on efficiency.

METHODS

Participants

Nine healthy adults (including two authors, J.H. and C.M.) participated in the experiment. All had normal or corrected-to-normal vision. Five participants were women, and all were aged between 24 and 44 years.

Apparatus

The experiment was run using Matlab (with Psychophysics toolbox; Brainard, 1997) to control presentation of the visual stimuli on a 17-in. CRT computer monitor (Nokia Microemission Valuegraph 447W, 1024 × 768 pixels, refresh rate = 75 Hz, mean luminance of mid gray = 93 lx at 0 cm). The program included a gamma correction ($\gamma = 2$) to correct for nonlinearity in the monitor luminance. TMS was applied using a Magstim SuperRapid stimulator (Magstim, Withland, UK) and a figure-of-eight double 70-mm coil, which can induce a maximum magnetic field of 2.2 Tesla at the scalp site. The Matlab program that controlled stimulus presentations also triggered the TMS pulse. The TMS pulses were triggered between screen-refresh cycles, thus preventing any visible artifact on the monitor induced by the magnetic pulse.

Stimuli

The target stimulus was a gray-scale sinusoidal luminance grating (spatial frequency = 1.6 cycles/deg), spatially modulated in contrast by a Gaussian envelope (1.4° full width at half height), tilted ±45° and presented with random spatial phase on a mid-gray background for 3 frames (40 msec) and viewed at a distance of 57 cm. Image noise was added as dots (single pixels) with random luminance sampled from a rectangular distribution (therefore, the variance of this noise equals one twelfth of its maximum contrast).

Procedure

Before commencing the experiment, each participant was tested to determine the location of phosphenes induced by single pulses of TMS delivered to the left occipital pole (approximately 1 cm above and to the left of the inion). The position of the coil, and amplitude of stimulation output, was varied to find the location and lowest intensity that could reliably induce phosphenes (with the participant's eyes closed and ambient illumination kept low). Participants then received further TMS pulses while they fixated on a dot in the center of a sheet of paper placed over the computer monitor. On these trials, they were asked to draw the position and size of the perceived phosphene on the paper.

During the experiment, the participants performed a forced-choice task to report the orientation (left vs. right) of a visual grating (see Figure 1). The location of the grating varied between participants—its position corresponded to the center of the phosphene as reported by the participant before commencing the experiment. On each trial, the TMS pulse was triggered almost exactly 100 msec after presentation of the grating (the pulse was triggered exactly 8 frames after the beginning of the first frame that contained the grating, which would give a grating-TMS asynchrony equal to 106.6 msec [8 frames] minus approximately 6.6 msec of the first frame before the stimulus actually appeared in the lower half of the screen). The amplitude of the pulse was 110% of the phosphene threshold for that participant (between 72% and 90% maximum output).

During 30-trial test blocks, the grating contrast was varied according to an adaptive staircase procedure (Kontsevich & Tyler, 1999) to measure the participant's discrimination threshold (i.e., the contrast at which the grating orientation was detected with 81.6% accuracy). The participants completed multiple blocks in a factorial design. Factor 1 varied the site of TMS: A single pulse of TMS, at 110% phosphene threshold, was delivered to the occipital pole (visual cortex) or a control site (Cz). The TMS pulse was delivered 100 msec after presentation of the grating. Factor 2 varied the amount of image noise added to the visual stimulus: Participants were tested with either three, four, or five different levels of random-dot noise superimposed on the grating. Three participants (C.M., J.H., and I.H.) completed four blocks for each of 10 conditions (5 levels of noise × 2 TMS sites). The other six participants completed two blocks for each of six or eight conditions (TMS to the visual cortex or Cz, and three or four levels of image noise). Six participants (C.M., J.H., I.H., R.M., M.S., and C.R.) additionally completed two or three blocks without TMS or image noise to serve as a baseline against which to assess the effects of TMS delivered to the control site Cz. This established that TMS to Cz did not change discrimination thresholds: The mean T^2 values obtained with no TMS and when TMS was applied to Cz were 0.00093 and 0.00087, respectively ($t = 1.07, p = .36$).

Analysis

The stimulus strength (the measured threshold, T) was expressed in terms of contrast on a scale from 0 to 1, and is thus on the same scale as the image noise. For example, a contrast threshold of 0.01 meant that the lightest and darkest bands of the sine wave grating were 1% above and 1% below the mid-gray background. T is directly (linearly) related to the total level of noise (i.e., from external and internal sources) expressed in *SD* units (Green & Swets, 1966). Therefore, T^2 (the contrast threshold power) is linearly related to the variance (SD^2) of the total noise. It is convenient to express noise in this way because when two or more independent sources of noise are combined their variances add (i.e., the total variance = the sum of the component variances). Therefore, the variance of the image noise will add to the variance of the internal noise (noise in the participant's sensory systems), and therefore, T^2 will be linearly related to the variance of the image noise. Moreover, if TMS makes an additional independent contribution to the total noise, its variance will add to the other sources of variance such that T^2 will increase by a constant amount. In other words, an effect of TMS on noise will be observable as a parallel shift in the line relating T^2 to image noise.

RESULTS

The location of the phosphenes induced before testing, and thus, the position of the grating stimulus during testing, varied between participants but was always in the lower left quadrant of visual field. The center of the stimulus was between 2° and 11° eccentricity (2° to 10° horizontally; 0° to 5° vertically). Differences between participants in the position of the stimulus did not correlate (rs $< .1$) with the effects of TMS (described below).

The results of principal interest are presented in Figure 3, plotting each participant's T^2 against the variance of image noise. As expected, thresholds increased with increasing image noise, and in each participant the

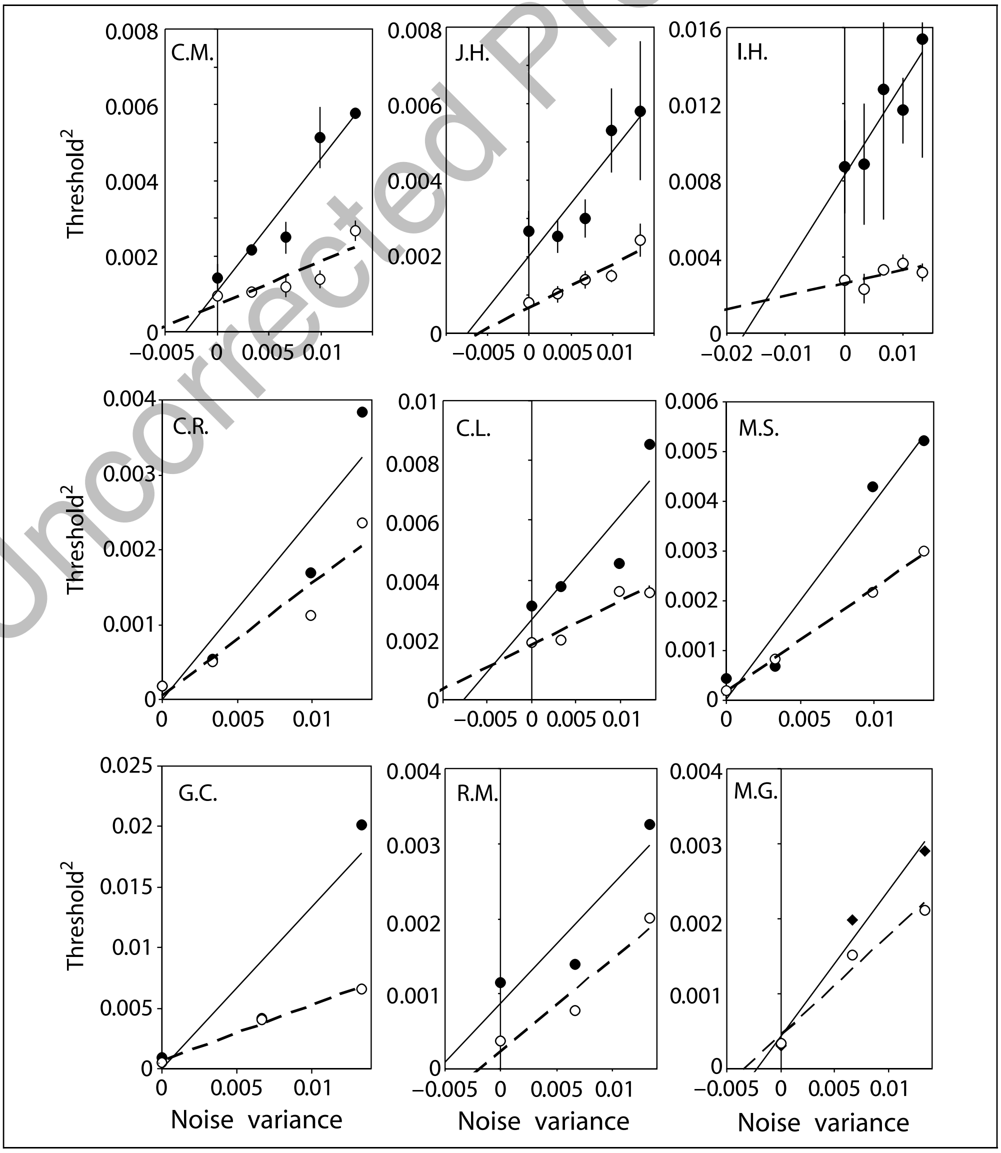


Figure 3. Squared detection thresholds (contrast power), plotted against variance of image noise, for each of the nine participants. Threshold contrast power was higher, and the slope of the regression line was steeper, when TMS was delivered to the visual cortex (black circles and solid line) than to the control site (Cz, white circles and dashed line).

relationship between T^2 and image variance was well approximated by a straight line. The results also show clearly that TMS to the visual cortex elevated visual detection thresholds, a finding that is consistent with several previous reports (Kammer, Puls, Strasburger, Hill, & Wichmann, 2005; Amassian et al., 1989). The key observation from these data is the interaction between the effects of TMS and image noise. Specifically, the relationship between image noise and T^2 differed for the two TMS conditions: For every subject, the slope of the linear regression was greater when TMS was applied over the visual cortex than when TMS was delivered at the control site. Table 1 presents the regression slopes and the ratio of the slopes from the two TMS conditions. Compared to the control site, TMS over the visual cortex increased the slope more than twofold on average (mean = 2.7; median = 2.36). This difference between the two conditions is statistically significant (Wilcoxon signed-rank test, $z = 2.67$, $p = .008$).

The best-fitting regression lines in Figure 3 are projected backward to show their *X*-intercept (see Table 1), and thus, provide an estimate of the variance of the participant's internal noise (i.e., all sources of noise other than that added to the stimulus image). If TMS applied to the visual cortex added noise to the visual processing, this should have produced a leftward shift in the function relating T^2 to image noise (i.e., a more negative intercept). However, a leftward shift was observed for only one (R.M.) of the nine participants (a second participant, J.H., showed a very small leftward shift). Indeed, when we calculated the goodness-of-fit for regression lines that had the same *X*-intercept (i.e., assuming zero shift between VC-TMS and Cz-TMS data), the R^2 values were almost identical to those calculated for regression lines with different intercepts (see right columns of Table 1). For each of the nine participants, there was no difference in the goodness-of-fit of the regression lines derived using a single *X*-intercept versus two intercepts (all *F*s < 1; Dobson, 1990). This effectively rules out evidence for any shift between the two conditions.

DISCUSSION

The present experiment used a classical added-noise paradigm (Pelli & Farell, 1999) in a simple visual detection task to distinguish between two possible accounts of the functional impact of TMS on neural processing: (1) that TMS interrupts signal processing to reduce signal strength; or (2) that TMS adds noise to that process. These accounts differ in their predictions as to how the effect of TMS will interact with noise added to the visual image. If TMS of the visual cortex interrupts visual processing, and thereby reduces the effective strength of the visual signal, this will interact with the image noise in a multiplicative manner. If, on the other hand, TMS of the visual cortex adds random noise to visual processing, then its effect should combine in an additive way with the impact of the image noise.

The results of our experiment provide robust evidence to support the first proposal. Specifically, TMS of the visual cortex reliably increased the slope of the line relating T^2 to image noise. This increase in slope reflects a decrease in efficiency of the visual system, and can be attributed to decrease in the strength of the visual signal. Although the magnitude of the effect varied considerably between subjects, the typical effect of TMS was to more than double the slope between image noise and T^2, which implies a halving of efficiency (a 50% reduction of signal strength relative to noise).

In contrast to its support for the hypothesis that TMS interrupts neural processing, our experiment provided no support for the second hypothesis that TMS adds noise to neural processing. Evidence for this hypothesis would be obtained if TMS had induced a leftward shift in the function relating threshold power (T^2) to image noise. However, only two of nine subjects showed any

Table 1. Slopes (±*SEM*), *X*-intercepts, and R^2 for Linear Regression of Threshold Data under VC-TMS and Cz-TMS Conditions for Each Participant

Participant	*Slope VC-TMS*	*Slope CZ-TMS*	*Slope Ratio*	*Intercept VC-TMS*	*Intercept Cz-TMS*	*Intercept Difference*	*R^2 (Separate Intercepts)*	*R^2 (Common Intercept)*
C.M.	0.35 (0.06)	0.11 (0.04)	3.07	−0.003	−0.005	0.002	.928	.920
J.H.	0.27 (0.07)	0.11 (0.02)	2.44	−0.008	−0.006	−0.001	.931	.930
I.H.	0.49 (0.13)	0.07 (0.04)	7.27	−0.017	−0.039	0.022	.926	.926
C.R.	0.25 (0.07)	0.15 (0.04)	1.61	0.000	0.000	0.000	.889	.888
C.L.	0.35 (0.14)	0.15 (0.03)	2.36	−0.008	−0.012	0.004	.851	.850
M.S.	0.40 (0.06)	0.21 (0.01)	1.90	0.000	−0.001	0.001	.971	.969
G.C.	1.44 (0.55)	0.46 (0.04)	2.61	0.001	−0.002	0.002	.877	.871
R.M.	0.16 (0.07)	0.12 (0.05)	1.28	−0.006	−0.002	−0.004	.875	.855
M.G.	0.20 (0.03)	0.13 (0.03)	1.47	−0.002	−0.003	0.001	.972	.970

shift at all, and one of these shifts was negligible. Moreover, the data of those subjects, as for the other seven, were well fitted by regression lines that assumed no leftward shift between TMS and control conditions. The simple addition of noise induced by TMS would predict a parallel shift in the line relating T^2 to image noise, rather than the observed increase in slope of that line. However, if TMS were to add noise after gain control operating on the signal and image noise, it could create an interaction between TMS noise and image noise (Dao et al., 2006), resulting in an increase in slope. Nonetheless, noise added in this way would also produce a leftward shift in the function relating T^2 to image noise, which was not observed.

It is worth considering the possibility that the image noise enhanced the effect of TMS to the visual cortex, rather than vice versa. This interpretation would be in keeping with evidence that voluntary movement can increase excitability of the motor cortex, augmenting motor evoked potentials elicited by TMS of the primary motor cortex (Mazzocchio, Rothwell, Day, & Thompson, 1994). However, this possibility is discounted by evidence that, unlike the motor cortex, the visual cortex becomes *less* sensitive to TMS when ''primed'' by a visual stimulus (Rauschecker, Bestmann, Walsh, & Thilo, 2004). Specifically, these researchers showed that a visual stimulus increases the stimulation threshold required to induce a phosphene when a single pulse of TMS is delivered to the visual cortex. Therefore, the present observation that TMS interacted multiplicatively with image noise was in spite of, rather than because of, possible changes in cortical responsiveness to the TMS pulse, and in spite of a possible decrease in the induced phosphene.

As we have suggested above, one means by which TMS could reduce signal strength is by momentarily disabling neuronal function leading to a loss of whatever information was coded by the activity of the afflicted neurons. An alternative possibility is suggested by a very recent study by Silvanto, Muggleton, Cowey, and Walsh (2007) that measured the effects of TMS to the visual cortex of participants who had undergone adaptation to a color or to a colored grating. These researchers found that TMS selectively increased sensitivity in detecting the adapted color or colored grating, leading them to conclude that TMS preferentially excites neurons whose activity at that time is low. In other words, rather than inducing random neuronal activity, TMS may induce a pattern of neuronal activity that is the complement of the extant activity pattern because it has a greater effect on less active neurons, and less effect on more active neurons. If this conclusion can be extended beyond the adaptation paradigm used by Silvanto et al. and applied to the present paradigm, it means that the TMS-induced activity would effectively cancel the stimulus-induced pattern of activity that codes for the stimulus. That is, if the signal is coded as differential activity across the relevant population of neurons, with some neurons responding more strongly than others depending on the tuning of their input filters, TMS would reduce this difference in activity by making all neurons respond vigorously, thereby reducing the strength of the signal coded by that population of neurons. This explanation is consistent with the findings we present here.

In sum, the present data provide clear evidence that, in the perceptual task used here, the functional consequence of TMS is a loss of signal strength and not the addition of noise to signal processing. It will, of course, be necessary to conduct similar investigations in other behavioral paradigms in order to test the generality of this conclusion. The important contribution of the present article is to show how this can be achieved. The logic of the added-noise procedure we have used derives directly from a signal detection framework (Green & Swets, 1966) that can be applied to any type of decision task, and using any type of sensitivity index (e.g., accuracy, d', reaction times).

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