

Two Types of TMS-Induced Movement Variability After Stimulation of the Primary Motor Cortex

Timothy Verstynen,^{1,2} Talia Konkle,¹ and Richard B. Ivry^{1,2}

¹Department of Psychology and ²Helen Wills Neuroscience Institute, University of California, Berkeley, California

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Verstynen, Timothy, Talia Konkle, and Richard B. Ivry. Two types of TMS-induced movement variability after stimulation of the primary motor cortex. *J Neurophysiol* 96: 1018–1029, 2006. First published May 3, 2006; doi:10.1152/jn.01358.2005. Using transcranial magnetic stimulation, we studied the role of the primary motor cortex (M1) in repetitive movements, examining whether the functional contribution of this region is associated with controlling response timing, response implementation, or both. In two experiments, participants performed a rhythmic tapping task, attempting to produce isochronous intervals (range of 350–550 ms) while stimulation was applied over M1 or a control site. M1 stimulation was associated with increased variability of the inter-tap intervals (ITI), and, by manipulating stimulation intensity, we identified two distinct changes in performance: a generalized increase in ITI variability and a delay in the subsequent response when the pulse fell within a restricted window prior to movement onset. Using a series of simulations, we demonstrate that the general increase in variability and the temporally specific delay reflect disruption of response implementation processes rather than an increase in noise associated with response timing.

INTRODUCTION

Repetitive movements have proven useful for investigating the mechanisms behind motor planning and execution (Keele and Ivry 1989). While people are facile in matching an externally specified rate, analyses of the temporal variability have provided insight into the underlying component processes. An important distinction has been made between variability associated with processes determining when a response should be produced (i.e., central timing systems) and variability associated with processes involved in executing that response (i.e., implementation systems) (see Vorberg and Wing 1996; Wing and Kristofferson 1973). Distinguishing these processes is of general importance to the study of motor control. For example, evaluating the errors that occur during movement can be useful in modifying a central representation of the motor plan if the error arises from noise in central planning systems (e.g., Kording and Wolpert 2004). If, however, the errors result from noisy response implementation, then adjustments to the central plan could lead to *poorer* performance.

Several analytic techniques have been developed to isolate variability arising from these two component processes (Ivry and Hazeltine 1995; Pressing 1998; Vorberg and Wing 1996). Assuming that these components are independent of each other, Wing and Kristofferson (1973) showed that implementation variability can be estimated by the covariance between successive intervals. By subtracting this estimate from total variability, the remainder provides an estimate of central vari-

ability. They termed this latter component, “clock” variability; however, it subsumes all processes upstream from the point of response implementation and thus a more appropriate label is “central” variability (see Ivry and Hazeltine 1995).

This distinction between central and implementation variability has been supported by studies of patients with various neurological disorders. Peripheral neuropathies selectively increase estimates of response implementation variability (Ivry and Keele 1989). In contrast, damage to the medial and lateral portions of the cerebellum selectively disrupts implementation and central variance, respectively (Ivry et al. 1988; see also, Franz et al. 1996) although alternative functional distinctions between subregions of the cerebellum have been proposed (Harrington et al. 2004). Although the performance of patients with cortical lesions has also been evaluated within the framework of the two-process model (Halsband et al. 1993; Harrington and Haaland 1999; Ivry and Keele 1989), these studies have excluded patients with lesions of the motor cortex given their hemiparesis. This leaves open the question of where the motor cortex fits within the dichotomy of central and implementation processes.

A priori, one might suppose that disruption of the motor cortex would selectively increase implementation variability given the density of the descending projections from the motor cortex to the spinal motor neurons (for review, see Geyer et al. 2000). However, recent physiological studies in animals (Graziano et al. 2002; Paninski et al. 2004) and humans (Karni et al. 1998; Muellebacher et al. 2002) point to a critical role of the primary motor cortex in motor planning and learning. These results leave open the possibility that the primary motor cortex may not simply function as the “marionette strings” for limb movements, but rather may also contribute to higher level computations required for selecting and planning coordinated actions such as movement timing. To evaluate the contribution of the primary motor cortex (M1) in response timing and execution, we used transcranial magnetic stimulation (TMS) to briefly disrupt M1 while participants produced repetitive finger movements.

METHODS

Participants

Twenty-one people (13 male, all right handed), including two of the authors, participated in the study. All of the participants except the authors were financially compensated for their time. The study was approved by the Committee for the Protection of Human Subjects at UC Berkeley.

Address for reprint requests and other correspondence: T. Verstynen, Dept. of Psychology, University of California, Berkeley, CA 94720 (E-mail: timothyv@gmail.com).

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Experimental task

While seated, participants tapped with their right index finger on a telegraph-style response key. The elbow and wrist were unconstrained. Movements were restricted to flexion-extension of the index finger, with the response box positioned on an adjacent table surface. Timing of the responses, pacing tones, and TMS pulses were controlled by a desktop computer with millisecond accuracy.

The basic trial schematic is shown in Fig. 1A. Each trial consisted of a synchronization phase followed by an unpaced phase. During synchronization, the participant tapped along with an auditory metronome (1,000 Hz, 10-ms duration) for 10 intervals. The metronome was then terminated, and the participant continued tapping until they had produced an additional 31 unpaced intervals. A long tone (100 Hz, 1,000 ms) signaled the end of the trial. Feedback at the end of the trial indicated the mean \pm SD of the inter-tap-intervals (ITIs).

TMS device

TMS was applied with a NeoPulse stimulator (NeoTonus) using a 70-mm, iron-cored, figure-8 coil (Epstein and Davey 2002). For M1 stimulation trials, the coil was placed over the scalp at the site optimal for eliciting motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle of the right hand and orientated at an $\sim 45^\circ$ angle from the midsagittal line. For control stimulation, the coil was placed over the scalp at approximately the medial junction of the occipital and parietal lobes (see Fig. 1B) with an orientation pointing directly to the frontal pole. This location was selected as a control given its posterior position to regions implicated in movement planning and control, especially under conditions without visual guidance (Medendorp et al. 2003).

Procedures for experiment 1

Eleven of the 21 participants were tested in *experiment 1*. These participants tapped at two target intervals: a fast pace (350 ms) and a slow pace (550 ms). The experiment was divided into two blocks, one for each target interval with the order of the two rates counterbalanced across participants. Each block consisted of 2 practice trials without TMS and 24 test trials with TMS. Half of the test trials involved stimulation over the M1 site and the other half over the control site (medial occipital lobe near the occipital-parietal junction, see Fig. 1B). The stimulation site for a given trial was randomly determined with the constraint that no more than two consecutive trials were at the same site. TMS was only applied during the unpaced phase. The inter-pulse intervals were selected at random from a uniform distribution ranging between 1 and 2.5 s. The timing of the pulses was independent of the participant's tapping responses.

Estimating the scalp location of the control site was performed using a magnetic resonance imaging (MRI)-based stereotaxic local-

ization system (BrainSight, Rogue-Research) that takes into account individual variation in brain anatomy. Participants who had participated in functional imaging studies at UC Berkeley and were willing to provide access to their anatomical MRI images were recruited. The optimal sites for M1 and control stimulation were marked and coil position was monitored throughout the experiment using the stereotaxic system.

To determine the stimulation level, the motor threshold was defined as the intensity required to produce $\geq 50 \mu\text{V}$ MEPs in the EMG traces from the FDI muscle at rest on 50% of the trials in a 10-trial series. The target TMS intensity was set at a level halfway between this threshold and the intensity required to produce visually observable perturbations of the finger (range: 38–65% maximum stimulator output; MSO). Because this experiment was not designed to test the underlying physiological mechanisms mediating M1 TMS-induced tapping variability, we opted for this stimulation level as a compromise procedure to ensure that stimulation would produce descending volleys to the muscle while minimizing actual perturbations of the finger during tapping. Note that during the experiment, TMS was applied during active movement, whereas our threshold was determined at rest. If motor thresholds decrease during movement (Starr et al. 1988), one would expect consistent finger perturbations during the experiment. However, participants rarely reported experiencing an overt finger perturbation likely due to the fact that modulation of M1 excitability is considerably lower during rhythmic movements compared with discrete movements (Carroll et al. 2006).

Procedures for experiment 2

In *experiment 2*, three stimulation intensities were used to test the effects of stimulation level on tapping variability. To reduce variability in our threshold estimates, the active motor threshold was determined with the FDI contracted at 15% of maximum voluntary contraction. As with *experiment 1*, the motor threshold was determined as the point at which TMS pulses elicited a MEP in the FDI muscle on 50% of the trials. MEPs were easily identified visually as a transient increase over background EMG after the TMS pulse. Test stimulation intensities were set to 85%, (low; MSO range: 29–40%), 105% (medium; 35–48%), and 125% (high: 44–59%) of this threshold, giving six trial types (3 TMS intensity levels \times 2 stimulation sites). Participants tapped at a target interval of 450 ms for 10 blocks of six trials each. Each trial type was tested within a single block with the order of the trial types randomized. In addition, the TMS pulses were delivered less frequently than in *experiment 1* with an inter-pulse interval ranging uniformly between 1.5 and 3 s.

Given that the primary motor cortex can be functionally localized by monitoring distal muscle responses and that the location of the control site in *experiment 1* was found to be fairly consistent across subjects, we did not perform stereotaxic localization for *experiment 2*. The location of the control site in *experiment 2* was 10 cm posterior

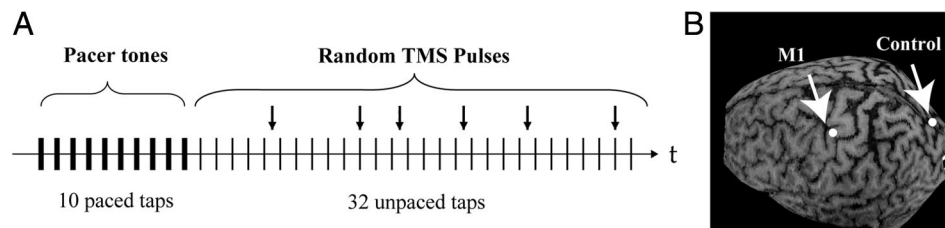


FIG. 1. Methods. A: each trial began with a series of 10 paced taps during which participants tapped in synchrony with a metronome. After this synchronization phase, participants produced an additional 32 taps without the metronome. During this unpaced period, transcranial magnetic stimulation (TMS) pulses were delivered over the primary motor cortex or a control site, the medial occipital-parietal junction. The timing of the TMS pulses was randomized so that the sounds from the stimulator would not form a competing rhythm. B: targeted cortical locations for stimulation shown on the magnetic resonance imaging (MRI) of 1 of the participants. In *experiment 1*, identification of the scalp position for the control region was determined on an individual basis using a stereotaxic localization system. In *experiment 2*, this position was estimated on the scalp relative to the vertex based on the average distance for participants in *experiment 1*. Primary motor cortex (M1) was identified functionally in both experiments. This position was marked on the anatomical MRI images for participants in *experiment 1* and used to maintain the position of the stimulator similar to what was done on control trials.

to the vertex (the mean position in *experiment 1*). As in *experiment 1*, stimulation over this region produced the same auditory and somatosensory effects as M1 stimulation but was not expected to influence tapping performance. Participants wore a cloth cap that was tightly fitted around the scalp on which the two stimulation sites were marked.

To relate the effect of TMS to movement phase within each cycle, EMG signals were recorded from FDI and the extensor indicis proprius (EIP) muscle throughout the experiment. Although not being the primary agonist for index finger tapping, FDI was chosen because it provides a stronger and cleaner EMG signal than deeper, extrinsic finger flexor muscles. Pilot tests revealed that FDI activation was coincident with flexion of the index finger. Participants were instructed to tap with a hand posture that maximized the EMG signal from both muscles, keeping their index finger relatively straight, and producing brisk downward strokes for each tap with a brief pause between taps. A third electrode was placed on the back of the neck to record the timing of the TMS pulses on the same traces as the EMG records. All EMG data were collected using bipolar surface electrodes (Delsy) and sampled at a rate of 4 kHz.

Data analysis

The data analysis was restricted to the 31 ITIs produced during the unpaced phase of each trial. Trials containing an ITI that was greater or less than 40% of the target interval were discarded on the assumption that these corresponded to unregistered taps or mechanical "bounces" of the response key. Four participants (2 in *experiment 1* and 2 in *experiment 2*) were excluded from the final analysis because they failed to produce at least six analyzable trials in one of the experimental conditions. For the remaining participants, on average 5% of trials were excluded.

Prior to estimation of the autocovariance functions, $\gamma(\cdot)$, the ITI time series for each trial was detrended based on a simple, least-squares linear regression. While this procedure creates a stationary time series of ITIs, the average regression coefficient was quite small, similar to that observed in previous studies with this number of intervals (see Madison 2001). Thus the detrending procedure had minimal effect on the component estimates. The function $\gamma(\cdot)$ was estimated using an autocovariance routine in MATLAB which scales the crosscovariance function by the inverse of the number of lags (i.e., $-1/5$). No correction was performed for potential bias in the autocovariance estimators. Following the Wing-Kristofferson model (1973), estimates of the total variance ($\gamma(0)$), response-implementation component ($\gamma(1)$) and central-timer component ($\gamma(0) - 2^*\gamma(1)$) were then calculated.

The EMG signals in *experiment 2* were rectified and low-pass filtered (5 Hz) using a Butterworth filter. The timing of the TMS pulses was identified from the neck electrode using a criterion that a TMS pulse occurred when the signal exceeded 3 SDs from the background noise of the EMG signal. Intensity of the EMG signal prior to each pulse was estimated by taking the root mean square (RMS) of first 40 samples (10 ms) prior to the pulse. The data collected from the response key were aligned to the EMG signals by co-registering the time stamps of the first TMS pulse in each trial and visually confirming the alignment of the two series.

The effects of condition on total and component variances were determined using simple univariate ANOVA with either total, central, or implementation variances as the dependent variables. When needed, paired sample *t*-tests were used for post hoc analyses to assess the effects of TMS stimulation.

Simulation procedure

Computer simulations were conducted to model the increase in variability induced by TMS stimulation of the motor cortex. The two-process Wing-Kristofferson model formed the basis of all of the

simulated models with variations added to test different ways in which TMS might disrupt performance. There were a total of seven fixed parameters in the simulation, although some parameters were set to zero for certain models. Two of the parameters were based on our experimental design: each simulated time series consisted of 1) 32 taps or 31 intervals and 2) the frequency of the simulated TMS pulses was based on the same algorithm as in the experiment. Three parameters were required to simulate the basic model: these included: 3) the variance of the implementation component, 4) the variance of the central component, and 5) the correlation θ , between adjacent implementation responses. Values for these parameters were taken from the group averaged data of the control condition in *experiment 2*. Two parameters were used to model the effects of TMS: 6) the local-delay function used to calculate the TMS-induced delay as a function of the time between the previous tap and the TMS pulse; and 7) the general increase in variance, calculated as the residual variance after the local-delay has been taken into account. These parameters were obtained from the group averaged data of the M1 condition in *experiment 2* (see ITI analysis).

A trial was simulated by generating a set of 31 intervals, where each interval was defined as

$$ITI = C_t + R_t^* - R_{t-1}^*$$

The terms C_t and R_t are normal random variables, corresponding to the time between centrally emitted control signals and implementation time of these commands respectively. Each interval is composed of one central interval and two implementation times, corresponding to the taps that initiate and terminate that interval. The notation R_t^* refers to the fact that successive implementation samples may be correlated, $R_{t+1}^* = R_t + \theta R_t^*$ (Wing 1977). The standard Wing and Kristofferson model assumes that $\theta = 0$.

We simulated 5,000 trials for each model. The autocovariance function was calculated by averaging across these simulated trials. After simulating the control condition to confirm the validity of the simulation procedure, six models were tested to evaluate different ways in which TMS could increase variability. Each model was tested at two stimulation intensities, medium and high, with the effect of intensity restricted to the two TMS-related parameters. The root mean squared difference between the simulated and observed autocovariance functions for lags 0 through 5 was used as a goodness-of-fit measure.

RESULTS

Experiment 1: TMS over primary motor cortex increases tapping variability

The goal of the first experiment was to determine whether TMS stimulation of M1 would increase variability during repetitive tapping. Assuming that such an increase was observed, we sought to determine whether the effect was associated with increased noise in central processes, response implementation processes, or both. To this end, we analyzed total variability and component estimates using the two-process Wing-Kristofferson model (Wing and Kristofferson 1973).

Participants were able to accurately maintain the target rate once the metronome was terminated. Overall, the mean tapping interval during the unpaced phase was 344 and 529 ms for the control conditions, in which the metronome-defined interval was 350 and 550 ms respectively. TMS stimulation over the primary motor cortex (M1) did not produce a change in the mean tapping interval (fast pace = 344, slow pace = 528).

We first examined the data from the control conditions to assess their conformity to the basic assumptions of the Wing-Kristofferson model. As predicted by the model, the lag 1 was

negative for all 18 individual covariance functions (9 participants \times 2 rates). Moreover, for all lags >1 , the covariance did not significantly differ from zero for both the fast and slow rates (all P 's > 0.05). Given this, we used the standard two-process model to obtain estimates of central and implementation variability (Fig. 2).

As expected, total variability was greater for the longer interval, $F(1,8) = 32.93$, $P < 0.001$, replicating the well-established finding that timing variability increases as the mean produced interval increases (e.g., Gibbon et al. 1997; Ivry and Hazeltine 1995; Killeen and Weiss 1987). Moreover, the duration-dependent increase was limited to the estimate of central variability, $F(1,8) = 16.29$, $P < 0.004$. While the mean values suggest a similar relationship for the estimate of implementation variability, this value did not differ significantly between the slow and fast conditions, $F(1,8) = 3.59$, $P = 0.095$.

We next consider the effects of TMS on performance. A first concern is whether TMS produced any general changes in performance, independent of stimulation site. Although we did not include a no-stimulation control, performance during control stimulation in the current experiment was similar to that reported in previous studies using similar protocols (e.g., Ivry and Hazeltine 1995; Wing 1980;). Thus it does not appear as if there is a generalized disruptive effect of control TMS on performance.

TMS of M1 led to a significant increase in total variability, $F(1,8) = 6.21$, $P = 0.037$. In separate ANOVAs using the component estimates, this increase was only significant in the estimate of response implementation variability $F(1,8) = 13.71$, $P = 0.006$. The estimate of central variability did not increase after M1 stimulation, $F(1,6) < 1$, and the effect of rate did not interact with either estimate (implementation: $F(1, 8) = 4.57$, $P = 0.065$; central: $F(1,8) = 2.27$, $P = 0.17$; see Fig. 2B). Although neither the main effect nor the interaction were significant in the ANOVA involving the estimate of central variability, the means indicate that there may be an increase in central variability at the fastest rate. When paired t -tests were performed on the data for each rate separately, we did observe that M1 stimulation led to a significant increase in the estimate of central variability for the faster tapping rate, $t(8) = 2.47$, $P < 0.05$, but not for the slower tapping rate, $t(8) < 1$.

The primary finding of *experiment 1* is that M1 TMS increased the estimate of implementation variability. Moreover, this increase was independent of target duration. Thus it would appear that M1 should, within the context of repetitive timed movements, be considered downstream from central processes, including those associated with determining when the responses should be emitted. However, the conclusion that the effect is specific to implementation processes must be

qualified given that the post hoc analysis indicated that M1 stimulation also increased the estimate of central variability at the faster rate. Given this ambiguity, we adopted a more fine-grained analysis of the effect of M1 TMS in the following experiment.

Experiment 2: Intensity-dependent modulation of implementation variability

In the second experiment, we parametrically manipulated the intensity of TMS stimulation during repetitive tapping. We first established the active motor threshold with TMS and from this, defined three test intensity levels: 85, 105, and 125% of that threshold. Maximum stimulator output levels in the medium condition were generally similar to those levels that were used in *experiment 1*.

The low stimulation level should minimize, if not eliminate, overt perturbations of the finger; whereas, the high stimulation intensity should induce such perturbations. This latter condition provides a strong test of the hypothesis that M1 TMS selectively affects response implementation variability. Alternatively, at higher stimulation levels, central timing processes may also be affected, especially given that the participants are aware of the TMS-induced perturbations. We also monitored the EMG activity of the FDI and EIP muscles in *experiment 2*, providing an additional measure of how TMS alters the implementation of responses.

Given the additional conditions created by the intensity manipulation, a single target duration of 450 ms was used. Participants were accurate in matching their tapping rate to this pace. The mean tapping interval during the unpaced phase was 438 ms and TMS stimulation over M1 did not produce a change in the mean tapping interval compared with the control condition (432 ms).

In contrast to *experiment 1*, the autocovariance functions (ACVFs) of the ITIs failed to conform to the predictions of the basic Wing-Kristofferson model. Given the independence and open-loop assumptions of the basic model, the covariance function should be negative for lag 1 (adjacent intervals) and zero for all higher lags. However, in four of six conditions, the lag 2 covariance was significantly less than zero and the means were in the same direction for the other two conditions (see Fig. 3A). In fact, negative covariances were also observed at higher lags.

This pattern is consistent with a modified two-process model in which response implementation variance is positively correlated across trials (Wing 1977). Following this model, the ACVFs were used to estimate central and implementation variability and the degree of correlated implementation noise.

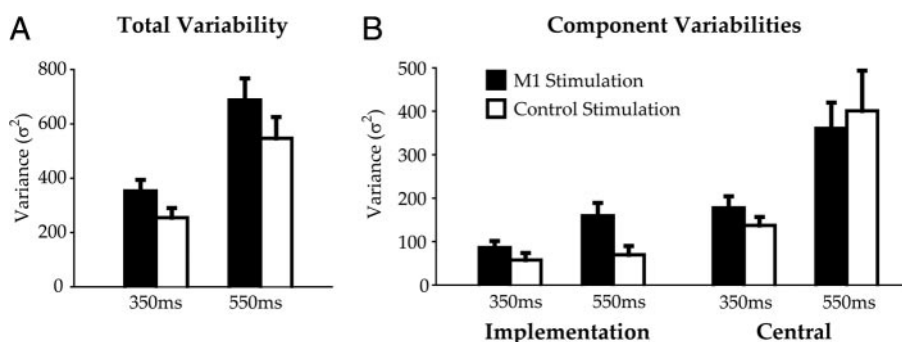


FIG. 2. Variability measures for *experiment 1*. A: variability of the inter-tap intervals for the fast (350 ms) and slow (550 ms) conditions. ■, stimulation over the M1; □, control stimulation. B: estimates of implementation and central sources of variability based on the Wing-Kristofferson method. Error bars are SE.

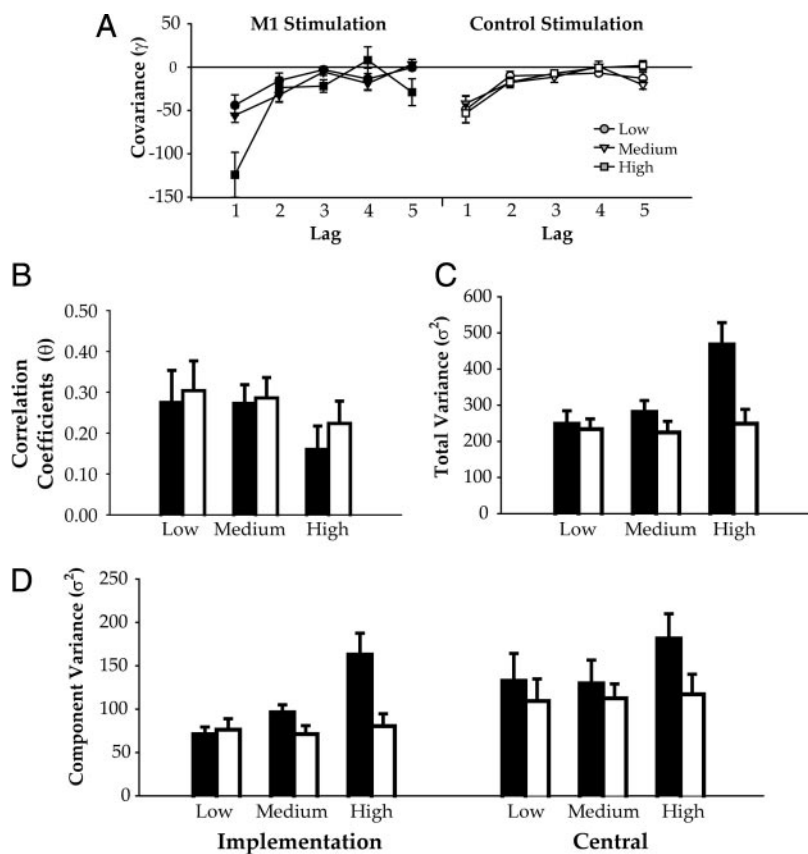


FIG. 3. Results from *experiment 2*. *A*: autocovariance functions for the 6 conditions. Note that the function is consistently negative at lag 2 in accordance with a model in which implementation variability is positively correlated across taps. *B*: estimates of the positive correlation between successive samples of the implementation distribution (■, motor cortex; □, control) across stimulation intensities. *C*: variability of the inter-tap intervals. *D*: estimates of implementation and central sources of variability based on the modified Wing-Kristofferson method.

This model provided a much better fit than the standard two-process model: averaged over all participants and conditions, there was an 87% decrease in summed-squared error between the predicted and observed ACVFs for the model with positively correlated implementation noise. Interestingly, the estimates of the correlation parameter were not affected by stimulation sites, $F(1,7) = 1.15$, $P = 0.32$, or stimulation intensity level, $F(2,14) = 2.10$, $P = 0.16$, and did not interact with these two variables, $F(2,14) < 1$ (see Fig. 3*B*). The introduction of positively correlated implementation noise in *experiment 2* likely results from the fact that we required the participants to adopt a constrained tapping mode (see Wing 1977) to maximize the movement-related EMG signals. Given the null effect of the experimental variables on the correlation parameter, all subsequent estimates of the component sources of variability are based on a modified two-process model in which implementation noise is assumed to be positively correlated.¹

Estimates of component sources of variability

Increasing stimulation intensity over M1 resulted in an increase in tapping variability when compared with control stimulation, $F(2, 14) = 14.00$, $P < 0.001$ (Fig. 3*C*). Individual paired-sample *t*-tests revealed that M1 TMS in-

creased total tapping variability with medium stimulation [$t(7) = 3.50$, $P < 0.01$], and high stimulation [$t(7) = 4.25$, $P < 0.01$] but not at the low stimulation level, $t(7) = 1.54$, $P > 0.10$. Thus overall tapping variability only showed significant effects of TMS with levels at or above motor threshold.

The component estimates are shown in Fig. 3*D*. Consistent with the hypothesis that M1 TMS introduces noise into processes associated with response implementation, higher stimulation intensities led to an increase in the estimates of implementation variability [intensity \times ROI interaction: $F(2,14) = 10.85$, $P = 0.001$]. At the high stimulation level, implementation variability increased by over 100% with M1 stimulation compared with the control site, $t(7) = 3.40$, $P < 0.01$. At the medium stimulation level, the increase was 35%, $t(7) = 3.65$, $P < 0.01$. In contrast, at the low stimulation level, the estimate of implementation variability did not vary between the two conditions, $t(7) = -0.84$.

M1 stimulation also produced a significant increase in the estimate of central variability, $F(1,7) = 18.06$, $P = 0.004$. Although the means indicate that this effect may be more pronounced for the higher intensity level, the interaction was not reliable, $F(2,14) = 1.25$, $P = 0.32$. Paired-sample *t*-tests revealed that the estimate of central variability for M1 TMS was significantly greater in the high-intensity condition, $t(7) = 2.36$, $P < 0.05$, but not in the medium, $t(7) = 1.00$, $P > 0.05$, or low $t(7) = 1.57$, $P > 0.05$, conditions. Thus M1 stimulation, at least at relatively high-intensity levels, appears to disrupt processes associated with both central planning and response implementation.

¹The lag-2 covariance [$\gamma(2)$] for the M1 condition at the fast rate in *experiment 1* was also significantly < 0 . We re-calculated the estimates of central and implementation variability for that experiment, using the correlated implementation noise model. Although these new estimates increase the proportion of variance associated with implementation processes, the overall pattern of results was unchanged from that based on the basic two-process model.

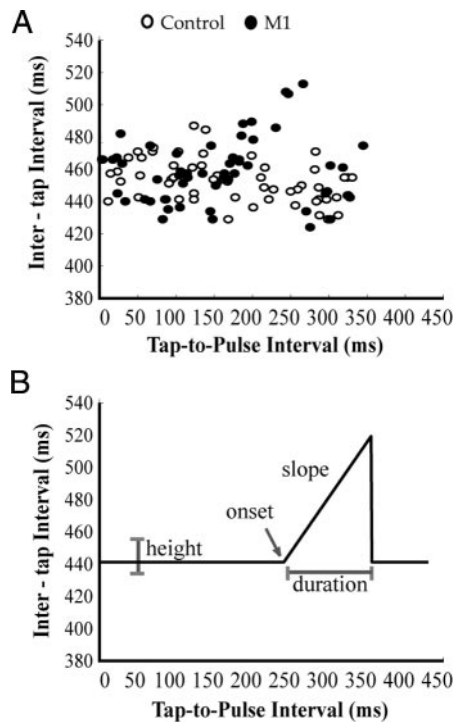


FIG. 4. Quantifying the TMS-induced delay. *A*: distribution of the inter-tap intervals (ITIs) as a function of time within the interval at which the TMS pulse was delivered. Data are from a single participant (●, M1; ○, control). *B*: plot depicting the average model parameters for the time-specific delay induced by high-intensity TMS stimulation. The parameter values are summarized and described in Table 1.

ITI analysis

The duration of ITIs that contain a high-intensity TMS pulse are plotted in Figs. 4*A* and 5*B* for two representative participants. The ITIs are presented as a function of the time between the tap that initiated the interval and when the TMS pulse was delivered (tap-to-pulse interval). When the M1 TMS pulse was delivered during the first 250 ms of the interval, there was little effect on the mean duration of the inter-tap interval. However, when an M1 TMS pulse occurred between 250 and 375 ms, the resulting ITI was lengthened. That is, the tap defining the end of the interval was delayed and the duration of this delay was proportional to the tap-to-pulse interval. Interestingly, TMS pulses that occurred just prior to the tap defining the end of the interval did not cause a delay.

The keypad data indicates that there is a critical period in which finger taps are susceptible to perturbation by motor cortex TMS. Further, the degree to which the IT is lengthened

is dependent on the timing of the TMS pulse within the critical window. To quantify this effect, we fit the series of ITIs to a model with four free parameters: *onset* and *duration* of the time window in which the ITI is susceptible to M1 TMS, *slope* of the TMS-induced delay; and *height* which corresponds to the average inter-tap interval produced outside of the critical period. These parameters were estimated using the Nelder-Mead simplex search algorithm (Legarias et al. 1998; *fminsearch* routine in Matlab R13) for each subject at each stimulation level and ROI. The average TMS-induced delay from high M1 stimulation is graphically represented in Fig. 4*B* and the parameter values for the medium and high stimulation intensities are summarized in Table 1. These indicate that across subjects, M1 TMS induced a delay ≤ 70 ms in the high-intensity condition and 30 ms in the medium intensity condition. Further, the degree of the perturbation (i.e., slope) and the duration of the effect were greater for the high stimulation compared with the medium condition. No perturbation was observed in the low stimulation condition or the control stimulation conditions.

Inspection of the EMG traces (Fig. 5*A*) suggests that the critical window for delaying the subsequent tap occurs prior to the onset of the flexor activity required for that response. That is, the interval may be lengthened because the high-intensity TMS pulses delay the onset of the flexors (Day et al. 1989). If this was true, then delayed responses would only be observed when stimulation occurs *before* the onset of FDI contraction; stimulation after FDI contraction should not lengthen the interval. Alternatively, TMS may also perturb the execution of an initiated response. If this was so, then delays might occur even when the TMS pulse occurs after flexor onset, perhaps due to disruption of flexor or extensor activity, or some combination of the two.

To examine this issue, we looked at the EMG activity on trials involving TMS pulses. As can be seen in Fig. 5*B*, EMG activity in the FDI just prior to TMS remained at baseline across the entire window within which the TMS pulses led to the lengthening of the interval. Indeed when we plot the ITI as a function of FDI activity just prior to the TMS pulse, we see that the long intervals are only observed when FDI EMG was extremely low; if flexion activation had been initiated, the interval duration was unaffected (Fig. 5*C*). Thus it appears that M1 stimulation lengthens the interval by delaying the onset of FDI rather than (or in addition to) disrupting on-going activity in the muscle.

Delaying the onset of a tap will, of course, lead to an increase of variability for the interval containing the TMS pulse. Of greater interest is the variability of the ITIs surround-

TABLE 1. Summary of the parameters used to quantify the two TMS effects

	Delay Parameters				General Increase, ms
	Onset, ms	Duration, ms	Slope	Height, ms	
High M1	243.0 \pm 13.3	104.4 \pm 10.4	0.67 \pm 0.06	440.6 \pm 6.3	7.3 \pm 2.0
Medium M1	225.1 \pm 25.0	77.6 \pm 26.2	0.43 \pm 0.07	439.1 \pm 4.4	3.7 \pm 2.1

The means \pm SE are given for the four free parameters describing the local delay. *Onset* and *duration* indicated the window in which transcranial magnetic stimulation (TMS) delays the subsequent tap. *Slope* reflects the relation between TMS stimulation in this window and the magnitude of the delay. *Height* indicates the duration of the intertap intervals (ITIs) outside of the window. The *general increase* parameter is the difference between the residual variability of ITIs with a primary motor cortex (M1) pulse (after the delay has been taken into account) and the variability of ITIs with a control pulse. All of the parameters in this table were used in the subsequent simulations of the TMS effects during tapping. The high stimulation delay parameters are graphically depicted in Fig. 4*B*.

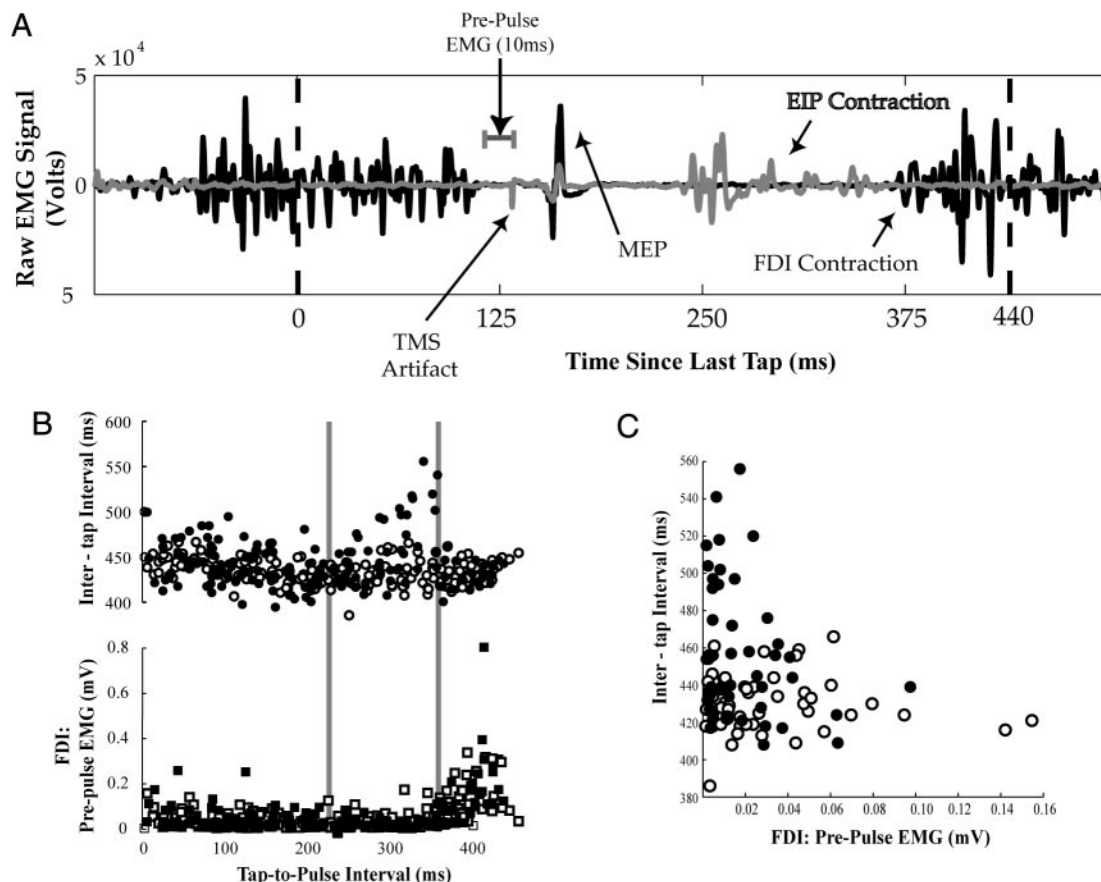


FIG. 5. Interval lengthening results from delay in electromyographic (EMG) onset. *A*: typical EMG traces for a representative interval [black trace, 1st dorsal interosseous (FDI); gray trace, extensor indicis proprius (EIP); dashed lines, keypress]. For each trial with a TMS pulse, background EMG was estimated over a 10 ms window prior to TMS onset. *B*, top: scatterplot of the duration of ITIs containing a high stimulation intensity TMS pulse, for 1 representative subject. ITIs are plotted as a function of the time between the initiating tap and the TMS pulse. Closed circles, ITIs with a motor cortex pulse; open circles, ITIs with a control TMS pulse. Gray bars, critical window as estimated by the model for this particular subject. *Bottom*: corresponding plot of EMG activity in FDI (squares) estimated just prior to the TMS pulse. *C*: correlation between background EMG of the FDI muscle and ITI duration for those trials within the critical window for the subject shown in *B*. Delayed intervals are only observed when EMG activity was still at baseline.

ing a pulse. In *experiment 2*, the frequency of TMS was adjusted so that a stimulation pulse was delivered approximately every four ITIs. This allows for a comparison of the ITIs before and after a TMS pulse (excluding any trials in which an $n - 1$ interval was also an $n + 2$ interval). If M1 stimulation selectively delays response implementation without affecting timing processes, there should be an increase in the variability of the subsequent ITI given that the delayed keypress also marks the onset on that interval. Alternatively, if M1 stimulation delays the central timing of the response, we would expect no increase in the variability of the interval after the TMS pulse given the assumption that central processes are independent of response implementation.

Figure 6A presents the variability of the ITIs for the high stimulation condition. These values are based on an average of 58 intervals per subject per condition. For the control stimulation site (\square), variability was constant across the surrounding intervals, indicating that generic factors such as the tactile or auditory effect of stimulation did not lead to increased variability in ITIs containing a TMS pulse compared with those without a TMS pulse. For M1 stimulation (\blacksquare), variability was elevated for all of the intervals, $F(3,42) = 8.07$, $P < 0.001$, which suggests that motor cortex TMS causes a general increase in tapping variability. In addition, this increase was

especially marked for the interval containing the TMS pulse, $t(7) = 5.16$, $P < 0.001$, and the following interval, $t(7) = 5.75$, $P < 0.001$, resulting in a significant interaction between region of stimulation and phase, $F(3,42) = 7.82$, $P < 0.001$. On intervals where a TMS pulse was delivered, the mean ITI was also increased (Fig. 6B), likely due to the local delay effect at the end of the interval. Interestingly, no changes in mean ITI durations were found for subsequent intervals.

The variability results suggest that M1 TMS adds two types of noise, one global, resulting in a general increase in variability, and a second local, restricted to the intervals marked by the response after the TMS pulse. Additional analyses provide further support for this dual effect hypothesis. Suppose that the only effect of M1 TMS was to delay a forthcoming response. After accounting for the delay induced in the critical window, residual variability should match that of the ITIs with control stimulation. However, we find that, after removing each subject's estimated TMS-induced delay, the residual variability of the ITIs with an M1 TMS pulse (Fig. 6, \blacksquare) remains elevated compared with the ITIs when TMS is applied over the control site. Moreover, the magnitude of the difference between the residual variability and control site values is similar to the amount of unaccounted variance estimated from the simple linear model of the delay effects (e.g., compare residual error

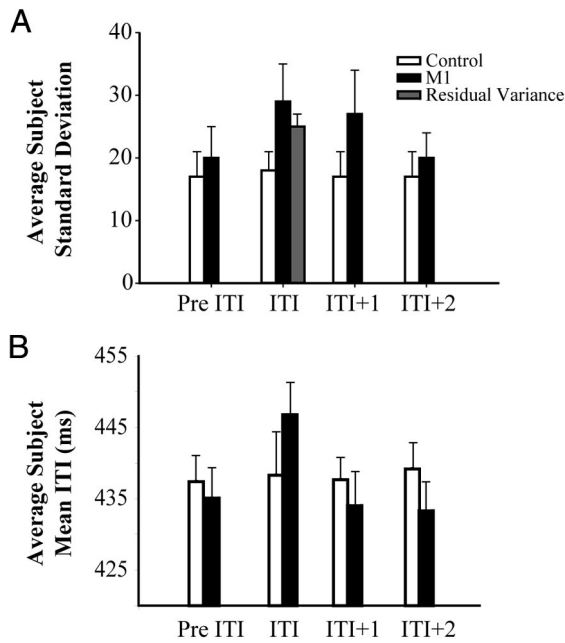


FIG. 6. Quantifying the increase in general variability across all intervals. *A*: plot of the SD in milliseconds of the ITIs before (pre ITI), during (ITI), and 2 intervals after a high stimulation intensity TMS pulse (ITI + 1, ITI + 2). □, ITIs surrounding and including control-TMS pulses; ■, ITIs surrounding and including M1-TMS pulses; ▨, residual variability of the ITIs in which a TMS pulse fell, after the delay effect was subtracted. *B*: plot of the mean interval duration for each ITI. Same conventions as *top panel*.

values in the top panel of Table 1 with Fig. 6). Similar effects, though less marked, were seen for the medium M1 stimulation condition as well.

In sum, the preceding analysis suggests that TMS over the motor cortex produces two effects on the distribution of the ITIs. First, if the TMS pulse occurs just prior to the rise in agonist activity, the forthcoming keypress will be delayed. Second, TMS over the M1 also causes a general increase in tapping variability beyond that produced by the local delay effect of the pulse. This increase is observed for all intervals, regardless of whether they follow or precede the TMS pulse.

Monte Carlo simulations

The estimates of central and implementation variability were both influenced by TMS stimulation. The implementation estimate increased with intensity, whereas the TMS-induced increase in the central component remained constant across stimulation levels. However, our microanalysis of ITIs revealed both a local and a generalized effect of M1 stimulation on tapping variability. The presence of these two types of changes may distort estimates of implementation and central noise obtained with the basic Wing-Kristofferson model. To explore this, we conducted a set of simulations.

For these simulations, we generated runs of ITIs where we simulated different ways in which M1 TMS might increase variability (see METHODS). To verify the reliability of this procedure, we first simulated the control data comparing two models: the basic two-process model (standard WK) and a modified model (Corr. WK) in which implementation noise is positively correlated (Wing 1977). As expected, the latter simulation provided a much better fit to the observed control ACVF (Table 2).

To simulate the effects of M1 TMS, we added in the effects of local and general TMS-induced noise. The local delay effect can be modeled in different ways. The pulse might solely affect implementation processes, perhaps by retarding the activation of the flexor and consequently delaying the execution of the finger tap. Alternatively, the pulse might solely affect central control processes. For example, central commands to initiate a finger tap might be delayed by the pulse. These models of TMS-induced delay have different implications on the pattern of the subsequent ITIs. Similarly, the generalized increase of variability in the ITIs could be put in either the central or implementation components. We thus end up with four models created by the factorial combination of local and generalized TMS-induced noise on either central or implementation components (see Fig. 7). Simulations were only conducted for the medium- and high-intensity conditions as there were no measurable TMS effects in the low-intensity condition.

The results of the simulations are shown in Table 2. The best-fitting model was the one in which the local and general effects of M1 TMS were associated with response implementation processes. Indeed, this model produced autocovariance functions that closely matched the magnitude of the observed covariance for each lag.

One concern with the simulation results presented in Table 2 is that even the best-fitting model of the M1 TMS data results in an inferior fit compared with the simulation of the control data. However, the control simulation fits may not provide an appropriate baseline because the simulated ACVFs are evaluated against the same data sets used to estimate the model parameters. These exact same parameters are then used to produce the M1 simulations with parameters added for the TMS effects. As such, the M1 model fits are subject to error both in the estimation of the TMS effects and in the parameters used to construct the models.

To provide a better estimate of what a true baseline model fit should look like, we conducted a split-half test on the control data. For each participant and each control condition, half of the trials were randomly assigned to an *estimation pool* and the other half allocated to a *validation pool*. The model parameters were obtained from the estimation pool and used to simulate autocovariance functions. These simulated autocovariance functions were then compared with the autocovariance functions of validation pool to provide a more reasonable baseline. For the estimation pool, the mean difference between the autocovariance functions for the simulated and observed time series ranged from 6 to 13 ms for the standard and corrected Wing-Kristofferson model in the high and medium conditions, compared with a range of 3–9 ms with the full data set. When the simulated values from the estimation pool were compared with the autocovariance function for the validation pool, the mean differences rose to 11–22 ms. Note that the fits to the models with TMS-induced local and global implementation noise are in the same range as the validation pool fits in the split-half procedure.

It is important to note that the results of these simulations are at odds with those based on the Wing-Kristofferson model. Whereas the component estimates from the Wing-Kristofferson model had indicated that TMS affected both central and implementation processes, the simulations indicate that TMS only affected response implementation processes. Interestingly, we can take the best-fitting autocovariance function from

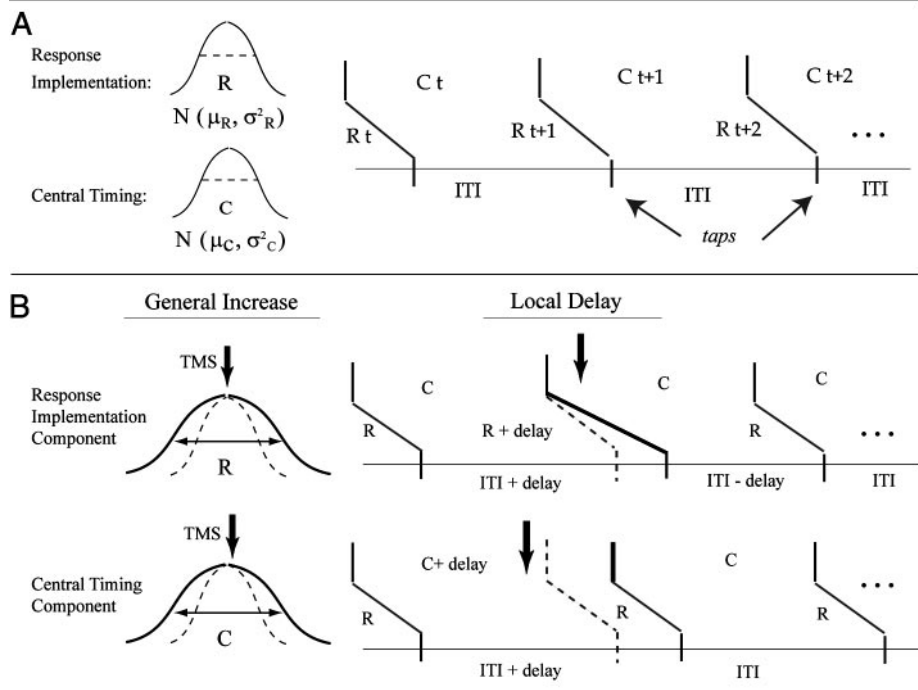


FIG. 7. Hypothetical models in which the local and general TMS-induced increases in variability are associated with either central or implementation processes. *A*: standard Wing-Kristofferson model is shown in the *top panel*. Each ITI is defined by 1 central interval and 2 implementation responses, where the duration of these events are based on samples from independent normal distributions. *B*: modeling the 2 effects of TMS-induced disruption of repetitive tapping. The generic TMS effect is modeled as an increase in the variance of the component distribution. The effect of the TMS-induced local delay may be restricted to interval containing the pulse or extend into the next interval.

the simulations in which *only* implementation noise was added and then re-analyze that data using the positively correlated Wing-Kristofferson model. When we do this, the standard Wing-Kristofferson estimates again indicate an increase in both central and implementation processes (M1 high: central = 145, implementation = 194; control high: central = 106, implementation = 90; M1 medium: central = 111, implementation = 95; control medium: central = 103, implementation = 78). Thus the simulation results provide a possible explanation for the elevated central component estimates obtained from the Wing-Kristofferson model. More importantly, the Monte Carlo simulations suggest that M1 TMS selectively introduces noise in two distinct ways to response implementation processes without affecting central timing processes.

Note that a post hoc analysis in *experiment 1* had indicated that M1 TMS increased the estimate of central variability for the faster tapping rate, in addition to the increase in implementation variability. It is likely that the two sources of motor noise identified in *experiment 2* also influenced the component estimates in *experiment 1*. However, a re-analysis of the results of *experiment 1* was not feasible given that the stimulation rate used was not optimal for obtaining reliable estimates of local delay and generalized variance parameters.

DISCUSSION

The M1 is at the interface between response planning and response execution. It is clear from neurophysiological studies that motor cortex activation is not strictly related to movement execution (for example, see Ehrsson et al. 2003). This fact might suggest an important role for the motor cortex in response planning processes such as central timing. While recognizing that a sharp dichotomy between planning and execution is simplistic, consideration of this division does offer a starting point for characterizing the functional role of motor cortex. Because it is difficult to test patients with lesions to this

area on the repetitive tapping task due to their hemiparesis, we opted to use TMS as an alternative method to produce transient disruption of the motor cortex.

The logic of our analyses is based on the two process model proposed by Wing and Kristofferson in which variability during repetitive tapping is assumed to reflect the sum of two component sources (Wing and Kristofferson 1973), one associated with central planning and the other associated with response implementation. We have demonstrated that threshold and suprathreshold TMS over the M1 increased temporal variability. Although an initial analysis with the Wing-Kristofferson model indicated that both central and implementation variability increased, at least with a high level of stimulation, our theoretical analyses point to a simpler account. Specifically, TMS-induced noise selectively affected the implementation system in two distinct ways. First, when applied during a restricted window, it delayed the implementation of a forthcoming tap. Second, TMS led to an increase in the general level of noise in the implementation system. Interestingly, these two forms of increased implementation noise can mimic an increase in central variability when estimated by the Wing and Kristofferson model. This point underscores the importance of analyzing tapping performance at both macroscopic (e.g., inter-interval) and microscopic (intra-interval) levels of analysis.

Two sources of response implementation variability during repetitive tapping

The delay in response execution following motor cortex TMS has also been observed in many studies involving discrete movements (Berardelli et al. 1994; Day et al. 1989; Leocani et al. 2000). In these studies, the duration of the delay was a function of stimulus intensity and was restricted to a window just prior to movement onset (McMillan et al. 2004). The repetitive tapping task provides a unique approach for analyz-

TABLE 2. Results of the Monte-Carlo Simulations

Condition	Autocovariance Function (Lags)					ACV Fits	
	1	2	3	4	5		
Control data							
High	249	-53	-17	-7	-1	2	—
Corr WK	247	-55	-17	-6	-3	-3	3
Standard WK	244	-55	-5	-4	-5	-3	6
Med	225	-42	-18	-11	1	-20	—
Corr WK	222	-43	-16	-7	-2	-3	7
Standard WK	217	-45	-5	-1	-3	-4	9
M1 data							
High	468	-124	-24	-22	8	-29	—
Imp Imp	473	-138	-39	-17	1	-1	15
Imp Cent	435	-106	-33	-14	-3	-2	20
Cent Impl	413	-92	-32	-14	-4	-1	29
Cent Cent	380	-62	-34	-13	-7	-4	46
Impl —	388	-107	-31	-14	0	-1	36
Cent —	332	-63	-24	-12	-3	-2	62
Med	282	-56	-32	-6	-19	3	—
Imp Imp	260	-56	-21	-7	-4	-2	12
Cent Imp	253	-51	-20	-7	-5	-2	14
Imp Cent	253	-50	-18	-8	-3	-3	15
Cen Cent	246	-45	-17	-8	-4	-4	18
Imp —	239	-49	-18	-8	-3	-3	20
Cen —	232	-44	-17	-7	-4	-4	23

Table 2: Results of the Monte-Carlo simulations. Control data: observed and simulated autocovariance functions (ACVFs) for the control stimulation data. Experimentally observed ACVFs for each condition are highlighted in bold. Below the bolded ACVFs for each condition are the estimated functions based on 5,000 simulated tapping trials using the standard Wing-Kristofferson model (standard WK) and the model with positively correlated motor noise (corr WK). M1 data: observed and simulated ACVFs for TMS stimulation over M1. Four models were simulated for both medium and high stimulation, using the initial estimates of central and implementation variances from the control conditions and then adding the local and general effects of M1 TMS into the central and implementation components. The last 2 rows give the average ACVF when only the local-delay effect is simulated. The ACV-fit column provides the root-mean-squared difference between the simulated and observed functions. This value represents the average deviation between two sites. The models for each condition are listed from best to worst fit.

ing the time course of this delay during continuous, self-guided movements given the uniform distribution of tap-to-pulse intervals. We observed a relatively narrow window of ~ 100 ms during which a delay could be induced, with the end of that window occurring just prior to flexion onset. The duration of the window is consistent with previous studies using discrete externally cued movements (Burle et al. 2002; Day et al. 1989).

It has been proposed that motor cortex stimulation retards movement onset by introducing a fixed delay in a serially organized response execution system (Burle et al. 2002; Day et al. 1989). This hypothesis predicts that the mean ITI duration would increase with TMS intensity, the width of the observed critical window would increase with TMS intensity, and the slope of this delay within the critical window would always be equal to 1 regardless of TMS intensity. Consistent with this model, we found that the response delay and duration of the critical window increased as a function of TMS intensity. However, contrary to the serial response process model, the slope of the delay function in the current study was greater in the high stimulation condition (0.7) compared with the medium stimulation condition (0.4). Thus our findings suggest that motor cortex stimulation does not delay movement onset by simply introducing a fixed interrupt in a serially organized system.

In addition to delaying the next tap, we also observed a second form of TMS-induced implementation noise. This source of noise was manifest as a generalized increased in tapping variability in both stimulated and nonstimulated intervals even after the effect of the local response delay is ac-

counted for (Fig. 6). In addition, simulations involving only the local delay underestimated the overall level of observed variability (Table 1). When we added a second, generic source of noise, we obtained excellent fits. By generic, we mean that the added variance in the model affected the implementation of all taps in a trial and was not dependent on the specific timing of the TMS pulse.

It is possible, however, that the true form of this additional motor noise is locked to the timing of the TMS pulse. For example, a single pulse can interfere with underlying cellular activity for many seconds beyond the pulse (Moliadz et al. 2003; Touge 2001). Given the frequency of TMS in the present study this generic noise may reflect a mild repetitive TMS (rTMS) effect on the motor cortex (Pascual-Leone et al. 1998). As shown in rTMS studies, the activity of the underlying tissue may be altered for an extended period of time after repetitive stimulation.

Interestingly, Doumas et al. (2005) reported that repetitive off-line TMS of M1 reduced asynchrony during paced tapping. That is, the phase lead of the finger with respect to the metronome signal was reduced. This was interpreted as showing a change in feedback-related processes. However, M1 rTMS may not affect the command to initiate each tap but could delay the implementation of these commands because of reduced motor cortex excitability. This alternative account is consistent with our hypothesis that M1 stimulation selectively affects implementation processes. Nonetheless, in contrast to the current results, Doumas et al. did not observe an increase in the variability of the inter-tap intervals (see also Theoret et al.

2001). Whether this lack of agreement is related to methodological differences or indicates that the generic noise effect is not a mild form of rTMS-effect is a subject for future investigation.

Physiological basis of the two types of TMS-induced noise

One explanation for the delay in response execution is that the refractory period of spinal motoneurons after a TMS pulse, renders them transiently nonresponsive to descending signals from M1. However, Day et al. (1989) demonstrated that a second TMS pulse delivered during the period of stimulation-induced delay was capable of producing a muscle response. They concluded that the response delay occurs at the level of the motor cortex. At a physiological level, they proposed that the transmission of motor commands is transiently disrupted by inhibitory mechanisms in the motor cortex. Burle et al. (2002) also emphasized disruption within the motor cortex itself by the introduction of a refractory period in neurons that send descending motor commands to initiate the movement. Both hypotheses predict that the delay should be observed up until the start of EMG activity in the agonist muscle. Our findings are consistent with this hypothesis; however, as mentioned in the preceding text, the slope of our delay effect is inconsistent with the idea the disruption of a serially organized response execution system (Burle et al. 2002; Day et al. 1989).

Single-pulse TMS is known to produce long-term alterations in the base firing rates of activated neurons. For example, a single TMS pulse to primary visual cortex led to attenuated activity that lasted up to a few seconds after stimulation (Moliadz et al. 2003). This reduced firing rate is not the same as the short-term (~200 ms) refractory period that is observed after an M1 TMS pulse (for review, see Reid 2002). The general increase in variability during M1 TMS might reflect a similar, relatively long-lasting mechanism. If neural responsiveness is disrupted for a few seconds after each pulse, increased variability should be evident in almost all intervals given that stimulation was, on average, applied every five taps. Future work is required to determine the precise neurophysiological mechanisms mediating the two types of TMS-induced noise observed in the present study.

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