Transcranial Magnetic Stimulation in a Finger-tapping Task Separates Motor from Timing Mechanisms and Induces Frequency Doubling

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Abstract

■ We study the interplay between motor programs and their timing in the brain by using precise pulses of transcranial magnetic stimulation (TMS) applied to the primary motor cortex. The movement of the finger performing a tapping task is periodically perturbed in synchronization with a metronome. TMS perturbation can profoundly affect both the finger trajectory and its kinematics, but the tapping accuracy itself is surprisingly not affected. The motion of the finger during the TMS perturbation can be categorized into two abnormal behaviors that subjects were unaware of: a doubling of the frequency of the tap and a stalling of the finger for half the period. More stalls occurred as the tapping frequency increased. In addition, an enhancement of the velocity of the finger on its way up was observed. We conclude that the timing process involved in controlling the tapping movement is separate from the motor processes in charge of execution of the motor commands. We speculate that the TMS is causing a release of the motor plan ahead of time into activation mode. The observed doubles and stalls are then the result of an indirect interaction in the brain, making use of an existing motor plan to correct the preactivation and obtain the temporal goal of keeping the beat. ■

INTRODUCTION

Temporal control of motion requires both a motor program and a timing mechanism, and debate surrounds where it is located and how it operates (Ivry & Spencer, 2004). Two forms of timing processes are thought to exist in the brain. One type of mechanism for timing is a centralized ''internal clock,'' located, for example, in the cerebellum or basal ganglia (Ivry & Spencer, 2004; Rao et al., 1997). The second type of timing mechanism is a cooperative, emergent process that is distributed in the brain and emerges as a result of a specific task (Ivry & Spencer, 2004; Mauk & Buonomano, 2004). Finger tapping is a simple paradigm for studying such event timing, involving a repetitive motion that can be precisely monitored. It is considered a concatenation of discrete movements that is punctuated by events such as surface contact, rather than a continuous motion (Spencer, Ivry, & Zelaznik, 2005; Delignières, Lemoine, & Torre, 2004; Spencer, Zelaznik, Diedrichsen, & Ivry, 2003). The leading model for finger tapping (Wing & Kristofferson, 1973) proposes a central timekeeper that provides intervals of the appropriate length, triggering motor commands at the end of each interval. The model hypothesizes that the clock and motor functions are distinct, and may involve totally different brain areas.

Prevalent thought is that the motor program in finger tapping involves a chain of central processes that occur in a given order, resulting in the serial activation of muscles. Neurophysiological studies in the cerebral cortex have shown that although this chain model may be oversimplified, a serial order exists in the manner in which cells in different regions fire during motor planning and execution (Crammond & Kalaska, 2000; Shima, Mushiake, Saito, & Tanji, 1996).

External intervention during finger tapping was limited in the past to variations in timing (Praamstra, Turgeon, Hesse, Wing, & Perryer, 2003; Repp, 2001a, 2001b), contact time (Semjen & Summers, 2002) and mechanical perturbation (Kay, Saltzman, & Kelso, 1991), and mainly served to investigate the dynamical aspects of motion and of return to stability using error correction. The advent of transcranial magnetic stimulation (TMS) has enabled a richer approach and resulted in a number of insights on timing (Verstynen et al., 2006; Doumas, Praamstra, & Wing, 2005; Pascual-Leone, Brasil-Neto, Valls-Sole, Cohen, & Hallett, 1992; Pascual-Leone, Tormos, et al., 1992; Day et al., 1989), trajectory control (Desmurget et al., 1999), stability of motor states (Meyer-Lindenberg, Ziemann, Hajak, Cohen, & Berman, 2002), and motor information

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processing (Gerloff, Corwell, Chen, Hallett, & Cohen, 1997; Berardelli et al., 1994). The advantage of using TMS for intervention during finger tapping is its relatively localized application in the brain, its temporal precision, and its wide range of output powers.

In this article, we employ TMS to study the interplay between the primary motor cortex and the timing machinery in the brain. The TMS is applied to the motor cortex in a periodic fashion, in synchronization with the metronome governing the finger tapping. We follow the trajectory of the finger and investigate the influence of the external intervention on both the timing of the motion and the motor execution. We find that TMS enables the separation of timing and motor functions, and intervenes in a particularly interesting manner in the motor function.

METHODS

Subjects

The experiment was approved by the local institutional review board. Nine healthy right-handed subjects took part in this experiment (5 men, age 20–48 years, mean 29.3 ± 8.7) after screening with the safety questionnaire (Keel, Smith, & Wassermann, 2000) and an EEG test. Two of the subjects are authors and the remaining seven were paid for their participation.

Design

Figure 1 presents the experimental setup. Subjects sat comfortably on a chair with their dominant hand resting on a pad so that the whole hand could rest comfortably as the finger was tapping. A photodiode was fixed into the pad so that the finger allowed light to enter it in proportion to its height above the pad (see Figure 1 and details below). The subjects wore headphones and heard clicks with a duration 5 msec of a metronome produced via the computer. All subjects were tested at 2.5 Hz, and some ($n = 7$) were tested also at other frequencies, ranging between 2 and 4 Hz. These rates were chosen because a tapping rate of 2–3.5 Hz is considered ''natural'' for most people (Collyer, Broadbent, & Church, 1994; Stevens, 1886).

Subjects were asked to tap to the beat as accurately as they can and to continue doing so even when perturbations to the finger are produced by the TMS. Subjects were explicitly told that their finger should be in contact with the target surface when they heard the metronome signal. They were also explicitly told to try to resist the perturbations and stay on beat. Subjects were not allowed to watch their tapping movement and, instead, were asked to fixate on a convenient point in front of them. At the end of each trial, subjects were asked to rate the perturbations they felt by giving a score from ''1'' to ''4.'' A score of ''1'' meant they felt no perturbation at all; ''2,'' that they felt something but it had no interference with the task; ''3,'' that the perturbation interfered with the task but they overcame the perturbation; and ''4,'' that they felt that the perturbation was so strong that they could not keep to the beat.

Every experimental session began with a pilot test prior to the experiment in order to determine seven TMS intensities that span the range of the ''1''–''4''

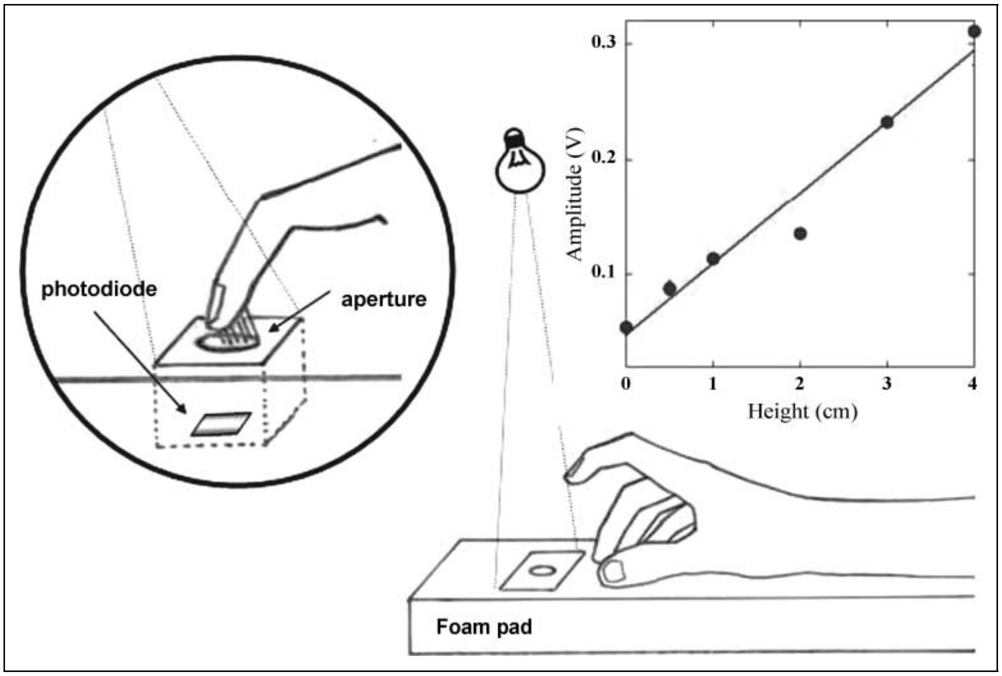

Figure 1. Finger measurement setup. Subjects sat comfortably on a chair with their dominant hand resting on a foam pad. A photodiode was positioned inside the pad, and a thin semitransparent tape covered the aperture of the photodiode box. An incandescent light was placed about half a meter above the photodiode, at a slight angle to it. When the finger was resting on the hole, it blocked the light from reaching the photodiode and a minimal current was obtained from it. As the finger detached from the pad and moved higher more light entered the hole (left inset), and the photodiode current increased. Right inset shows a calibration test for one subject. The finger height was linearly proportional to the photodiode output.

answers (see *TMS Parameters*). An experimental condition consisted of 21 to 35 trials, each comprising a continuous series of ∼50 taps. After several taps without TMS (no less than 16), the next 16 taps were accompanied by TMS. One pulse was given per tap, synchronized with the metronome beat and at a constant intensity. Subjects were asked at the end of each trial to give their subjective rating ("1"–"4"), and their answer was recorded. The next trial was carried out ∼20 sec later. At least three trials were performed at each of the seven chosen intensities, and the order of the intensities was determined pseudorandomly to avoid guessing of the next step by the subjects. In each session, a minimum of two and a maximum of three frequency conditions were tested with a 10- to 15-min break in between. The first frequency used in each session was 2.5 Hz. An interval of at least 1 week was given between sessions. Because the 2.5-Hz condition was always performed together with at least another condition, this condition was repeated for most subjects, and there were $n = 20$ conditions of 2.5 Hz.

In a control experiment, tapping without touching of the pad was executed with two of the subjects. An additional supporting block placed on the pad elevated the hand so that its motion brought it close to the pad at its lowest point but did not touch it. In this case, the photodiode gave only an approximate measure of the trajectory, and we added a video camera for precise measurement of the finger's motion. Analysis of the motion was then conducted off-line from a videotape.

Measurement of Finger Motion

We designed an efficient yet simple system for determining the finger position with good accuracy. A photodiode was positioned in the pad on which the finger was tapping so that it was viewing a small hole in the pad that was covered by a thin tape. An incandescent light was placed about half a meter above the photodiode, at a slight angle to it. When the finger was resting on the hole, it blocked the light from reaching the photodiode and a minimal current was obtained from it. As the finger detached from the pad and moved higher, more light entered the hole and the photodiode current increased. Calibration tests (see inset to Figure 1) showed that finger height was linearly proportional to the photodiode output. Estimate of the degree of accuracy in timing is 5 msec, and height accuracy is 1 mm. During the trial the photodiode output was visualized on a dedicated LabView program controlling the experiment, effectively giving a visualization of the actual trajectory of the finger.

TMS Parameters

Magnetic stimulation was delivered using a Magstim Rapid (Magstim Company, Wales, UK) magnetic stimulator with a 7-cm figure-of-eight coil. Motor-evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle using disposable surface electrodes. To determine the optimal site for activation of the index finger, we measured the resting motor threshold (rMT), which is defined as the minimal TMS energy needed to elicit five of ten 50-μV MEP responses (Pascual-Leone et al., 1998). The place of stimulation of the index finger was marked on a swimming cap that the subjects wore throughout the experiment. Because the rMT (when the finger is completely at rest and not tense) and the working motor threshold (when the finger is moving and the muscles are tense) are different, we performed a short pilot test in the beginning of each experiment. In this pilot test, subjects were asked to tap to a metronome at a rate of 2.5 Hz, and a train of 16 single TMS pulses (each of 200 μsec duration) time locked to the metronome click was applied. The intensities were distributed according to a random list around the predetermined rMT. The effect of the TMS on the finger was determined by inspection of the movement displayed on-line via the dedicated LabView control program and by the subjective rating "1"–"4" given by the subjects (see above). Based on this, a set of seven TMS intensities was chosen for each subject, spanning the range of no visualized or felt (subjective rating "1") perturbation all the way to a clear visualized and subjective rated "4" perturbation. These intensities varied across subjects and ranged from as low as 50% rMT to as much as 160% rMT. Intensities never exceeded the range of comfort for the subject (as reported by the subjects). The pilot tests were discarded from the subsequent analysis.

After each experimental condition, the subjects were given a 10- to 15-min break. The next condition was preceded by a measurement of rMT to determine that no change occurred in the tissue excitability (Pascual-Leone et al., 1998) during or after the experiment and to check that the position that stimulated the index finger did not change during the break. rMT that varied 2% of maximal TMS intensity or less above or below the initial rMT was considered unchanged. Similarly, the settings were considered unchanged if the location of activation for the index finger on the cap moved to a new spot inside a radius of 1 cm around the initial spot. In most cases, no change occurred at all.

In order to exclude an auditory effect, sham trials were performed in four subjects (one subject twice) at the end of the last trial of the last condition tested in the session. Four to five trains of TMS (∼16 pulses, intermittent with at least 16 taps without TMS) at the highest intensity were applied by placing a second, disconnected coil in the normal configuration with the connected coil positioned 4 cm directly above. In all cases, subjects reported feeling no perturbation to the finger.

All TMS parameters were in accordance with the recommended safety guidelines (Wassermann, 1998).

Recording and Analysis

A National Instruments A/D card (National Instruments, Austin, TX), together with National Instruments LabView software, was used to digitize and record the light information arriving from the photodiode. The same program was also used to create the metronome clicks, send the triggering signals to the TMS, and record the actual TMS stimulation. Data were analyzed using Matlab software (The MathWorks, Natick, MA). The points delineating the beginning and end of the periods where the finger was maximally flexed ("down" and touching the pad) and maximally extended ("up" position) were visually identified using a special Matlab program and marked by the experimenters. The tap cycle was divided into four parts: (1) finger at maximum extension, (2) finger flexing and on the way down, (3) finger at maximum flexion, and (4) finger extending and on the way up. Each tap was manually tagged 1–4, depending on where the metronome occurred between the maximum extension of the prior tap to the maximum extension of the current tap. Manual analysis was performed to avoid automatic analysis mistakes that arise due to variability in tapping between and within subjects.

Taps were considered accurate if the finger was in Phase 1 when the metronome struck. This criterion, although not the standard one for finger tapping tasks, fits best the requirement given to the subjects during the experiment. Subjects that were "off beat" more than 70% of the time were excluded from subsequent analysis. We defined "off beat" when the finger was in positions 2–4. This restriction excluded two subjects, one was usually at the maximally extended phase (position 3) when the metronome occurred, and the other was usually on the way down. About 3% of the total taps from accepted subjects were excluded from analysis because they could not be unambiguously categorized.

A complementary analysis was performed in parallel, using the standard deviation of the intertap interval (ITI), which is a more conventional measure of accuracy (Wing & Kristofferson, 1973). The beginning of the tap we defined as the first contact of the finger with the pad and the ITI was defined as the interval between the beginnings of two taps. The synchronization error was defined as the time between the beginning of each tap and the closest metronome pulse.

The existence of an additional minimum ("dip") in the finger trajectory in between the taps that occurred at or near the metronome beat indicated the existence of a "double." Both peaks flanking the dip had to be at least 50% of the average height of the regular peaks in the vicinity of the dip, and its time duration had to be at least 35 msec. The slopes of the dip had to be comparable to the slope of the peaks in its vicinity. The duration of each half of the double was counted from the two metronome beats to the minimum of the dip.

If during TMS application the time spent in a tap at the down position was longer than a given criterion, then that tap was defined as a "stall." The mean time of the down phase was first calculated for the no-TMS condition, and to qualify as a stall, the time spent down had to be both more than 150% of this mean, and more than two standard deviations longer than it.

Since each subject had a different range of the measured parameters (e.g., contact time, velocity, synchronization error) we calculated the average distributions by first normalizing the data with the individual average value of the parameter during the no-TMS condition. Probabilities were obtained from the individual histograms of each parameter. The average distribution of all the experiments presented in the different graphs was calculated by re-binning the data and averaging for each bin separately.

Statistical Analysis

The tests that were used to analyze the data in this study were two-sample one-tailed t test for independent samples, paired one-tailed t test, and randomized block design. Spearman correlation, which does not assume normal distributions, was used for all correlation analysis.

RESULTS

Transcranial magnetic stimulation was used as a means of perturbing the motor action of the finger while it was tapping to the beat of a metronome. TMS pulses were given together with the metronome clicks, in a train that included 16 pulses. Tapping without TMS perturbations served as a baseline.

Figure 2 shows the height of the finger as a function of time during the experiments at 2.5 Hz. Examples of the finger trajectory are displayed. Figure 2A demonstrates the baseline tapping motion of the finger when no TMS was applied and the period of tapping was 400 msec. Figure 2B and C demonstrates the two major scenarios for effects of TMS on finger motion. In the first case, the TMS caused the finger to stall at its lowest position for half a period and only then detach and perform the tap in the remaining half of the period (we call this kind of movement a "stall"). The mean duration across all subjects (defined as the time between the first point and last point of maximum flexion) of the time spent in contact with the pad during the regular, unperturbed tap was 106 (±9) msec, whereas the mean duration across all subjects of time spent on the pad during a stall was 199 (±10) msec, very close to 200 msec (no statistically significant difference was found from 200 msec, two-tailed t test, $p = .56$), which is half of the tapping period.

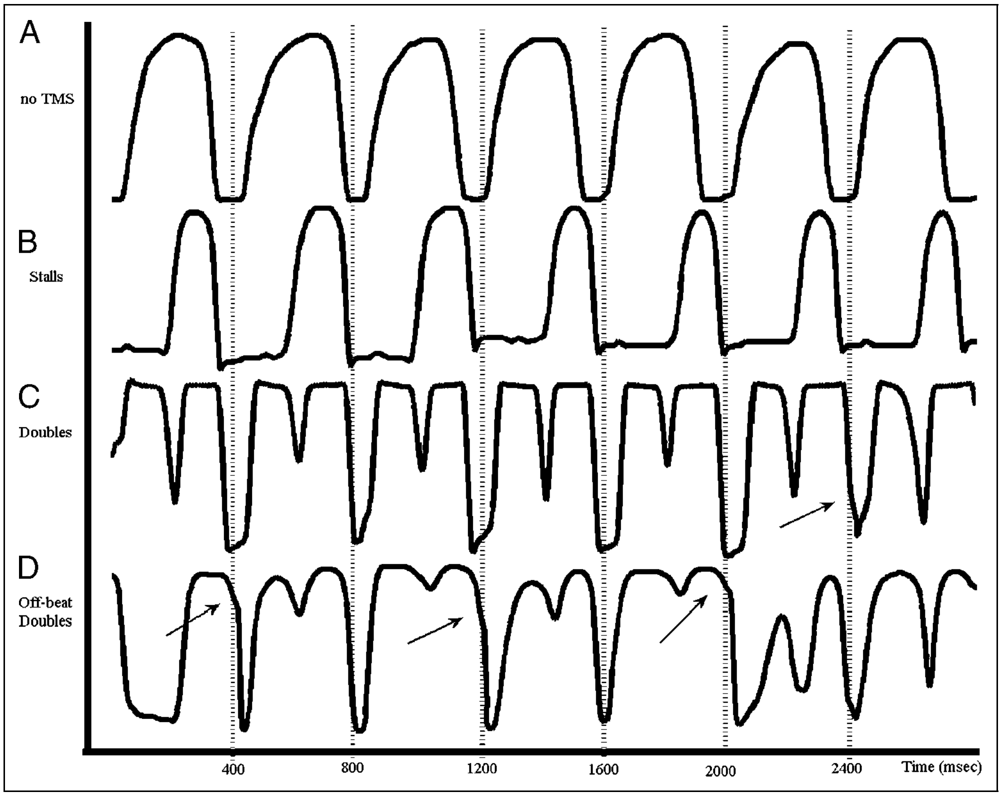

Figure 2. Tapping profiles. Finger height versus time for the three types of observed motion: (A) normal tapping without TMS, (B) the stall effect with TMS, in which the finger remains down much longer, and (C) the double motion with TMS, in which the finger taps at twice the required rate. (D) Examples of doubles occurring when subjects were off beat (indicated by arrows). There is no sharp deviation in motion as a result of TMS although the finger is moving, and subsequent taps are similar to those in part C). The dashed vertical lines are separated by 400 msec and indicate the times of metronome signals (A) as well as TMS pulses (B, C, and D).

In the second case, the TMS caused the finger to perform an extra tapping motion, although not necessarily completing the motion downward (we call this kind of movement a "double"). The frequency of the tapping was effectively doubled in this motion, with each tap extending one half of the metronome period. The mean durations across all subjects of the first and of the second taps were 212 (±7) msec and 186 (±7) msec, respectively, and they were not significantly different from 200 msec (two tailed t test, $p = .16$). Figure 2D shows that the doubling motion is unaltered when the TMS is delivered when the finger is still in motion. The arrows indicate off-beat finger positions (also in Figure 2C), which were usually on the way down at the time of the TMS strike (and metronome click). We see no difference in the motion completing the tap, and subsequent doubles or stalls appear the same as when TMS is given at the down position (on beat taps).

Table 1. Distribution of Doubles and Stalls across Intensities

	Intensity 1–2	*Intensity 3–5*	*Intensity 6–7*	*Intensity 1–7*
Stalls (%)	2.4 ± 0.9	8.0 ± 1.9	21.9 ± 4.4	11.2 ± 2.4
Doubles (%)	4.6 ± 2.4	12.2 ± 3.7	38.7 ± 7.3	17.3 ± 4.1

The first three columns display the average occurrence of doubles and stalls (mean and standard error) for the first two, middle three, and top two intensities, respectively. The last column displays the average occurrence of doubles and stalls for all intensities collapsed together.

Overall, the stalls and doubles occurred in 11.2% and 17.3%, respectively, of the taps where TMS was applied. Table 1 displays the mean occurrence of stalls, and doubles as a function of intensities, grouped into the low, medium, and high range. Occurrence of stalls increased with intensity from 2% to 22% for the lowest and highest intensities, respectively (see Table 1). Occurrence of doubles also increased with intensity, from ~5% at the low intensities up to ~39% for the highest intensities (Table 1).

In both cases, subjects were not aware of the precise nature of the abnormal movement of their finger. During doubles they reported feeling that the finger was "lighter" and "flying by itself," and during stalls they felt that the finger was "heavy" and "hard to move" at certain times. Defining a tap to be accurate if the finger is down at the time of the metronome click, we found that the subjective awareness of accuracy "1"–"4" reported by the subjects after every trial (see Methods) correlated well with their actual accuracy on each trial (Levit-Binnun, Handzy, Modai, Moses, & Peled, in press). The accuracy was measured relative to the train of taps without TMS preceding the TMS taps in each trial.

The structure in both doubles and stalls is interesting because both motions apparently divide the 400-msec time intervals into two parts of equal size. However, the second half of each effect consists of a tap which the subjects attempt to complete in 200 msec, albeit in the case of doubles they begin at a higher elevation. Effectively, this means that when performing doubles and

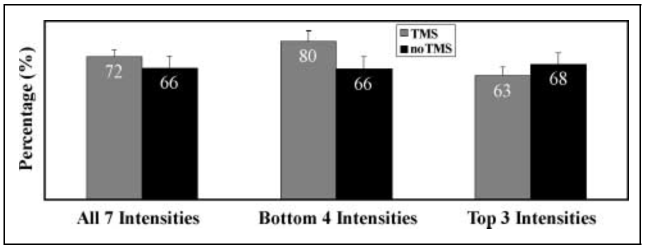

Figure 3. Tapping accuracy. Ratio of accurate taps to total taps performed without TMS (black columns) and with TMS pulses locked with the metronome signals (gray columns), for all subjects. A tap is considered accurate if the finger is down and in contact with the pad when the metronome signals. The leftmost columns show the tapping accuracy for all intensities. Middle columns show tapping accuracy for the lowest four intensities and the rightmost columns show the tapping accuracy for the highest three intensities.

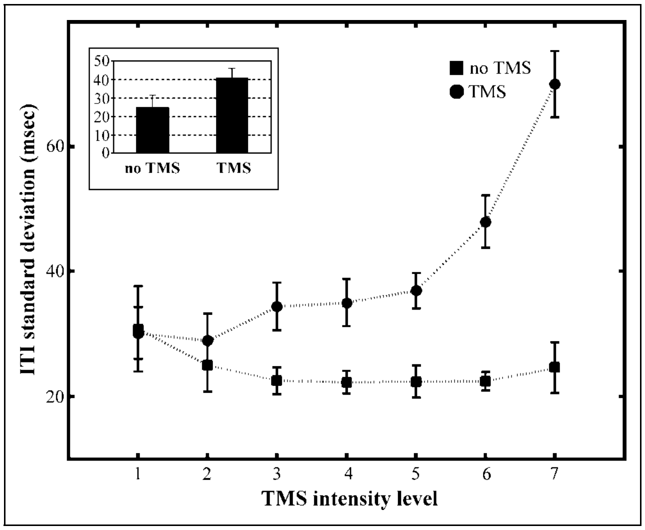

Figure 5. Variability of the intertap interval (ITI). The variability of the ITI, measured as the mean standard deviation of the ITI, as a function of the seven intensities for taps with TMS (circles) and taps without TMS (squares). Inset: The mean standard deviation of the ITI for TMS and no-TMS taps collapsed across all intensities.

stalls, the subjects are tapping at 5 Hz. One can reasonably expect the increased difficulty of this task to impair accuracy, but surprisingly, this was not the case. Figure 3 displays the percentage of accurate taps for both the unperturbed baseline and for the TMS perturbations (two left columns). TMS does not reduce the accuracy of tapping and, on the contrary, a slight increase is observed (see also Doumas et al., 2005), although the difference is not statistically significant (one tailed *t* test, $p = .15$). Interestingly, tapping accuracy remained high also when the finger performed stalls and doubles (see Figure 4, left-most columns).

Using the standard measures of accuracy, such as the variability in ITI and the synchronization error, gives a complementary view on these results. The ITI variability increases with TMS intensity (see Figure 5), which is linked to the variability in the motor execution and the strong fluctuations in the trajectory. On the other hand, the synchronization error becomes slightly less negative (see Figure 6) so that the tendency of the finger to touch the pad ahead of the metronome is smaller with TMS. This is in line with a slight improvement in accuracy during TMS.

Because doubles and stalls result in an effective increase of tap rate to 5 Hz, we analyzed data from the frequency study for accuracy as well. We found that without TMS, tapping accuracy did fall for all but one subject, when the metronome and tapping frequency increased from 2.0 to 3.0 Hz. The one anomalous subject was accurate 16.6% of the time at 2.0 Hz, and 46.1% at 3.0 Hz, and the average accuracy of the remaining six subjects decreased from 72.2% at 2.0 Hz to 34% at 3.0 Hz. We, therefore, find it surprising that the tapping accuracy of 66%, for all subjects at 2.5 Hz without TMS, does not decrease when TMS is given because doubles and stalls together account for 28.5% of all taps with TMS.

Information on the effect of TMS intensities can be obtained by looking at the distribution of tapping accuracy according to intensity. The middle and right columns in Figure 3 display the relative accuracy of tapping

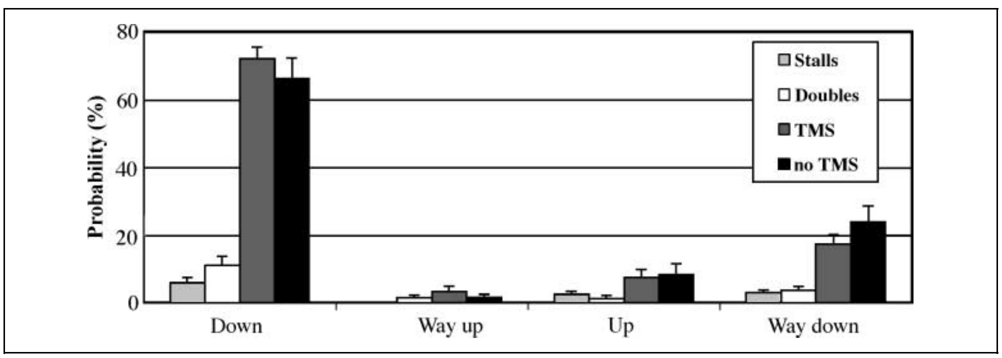

Figure 4. Probability of stalls and doubles to occur within the four phases of the tap cycle. If the subjects' finger was not down in time with the metronome, then their tapping was inaccurate and the metronome click occurred in other parts of the tapping cycle. This caused the TMS, which was locked to the metronome, also to be applied at times when the finger was not completely down. Shown is the division of the taps, for all subjects, according to where the metronome and TMS (when TMS was applied) occurred in the four different parts of the tap cycle (see Methods). Black columns: all the taps during no TMS; dark gray columns: all the taps during TMS; white columns: taps where doubles occurred after TMS was applied in the 4 phases; and light gray columns: taps where stalls occurred after TMS was applied in the 4 phases.

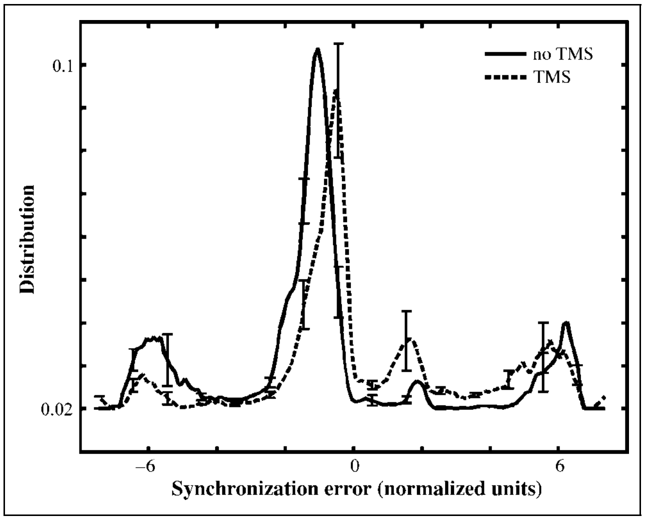

Figure 6. Distribution of synchronization error. The average distribution of the synchronization error, defined as the time between the occurrence of the metronome and the first touch of the pad for taps with no TMS (solid line) and taps with TMS (broken line). Distribution curves were normalized with the absolute of the mean error in the no-TMS taps. A clear shift of the synchronization error distribution peak from negative values toward zero is observed for the taps with TMS.

with and without TMS, but separated according to TMS intensities. The right columns show the three trials with high values of TMS intensities, and the middle ones show the four lower intensities. Although at the highest intensities there is no significant difference between the no-TMS and TMS conditions (one tailed *t* test, $p = .23$), at low TMS intensities the subjects were actually performing better on average (one tailed *t* test, $p = .002$).

Figure 7 demonstrates the possible irregularities in the trajectory of the finger during TMS. Figure 7A displays the overall distribution of contact durations for no-TMS and TMS taps for all subjects. Contact duration was defined as the time the finger was at the lowest position, that is, the interval from the time at which maximal flexion was attained to the time at which the finger started moving upward. Shorter contact durations correspond to doubles, whereas longer ones correspond to stalls. It is clear that during TMS the distribution broadens and there are both doubles and stalls. The distribution of stalls and doubles varied from subject to subject. Some subjects were more "stallers," whereas other subjects were more "doublers." Figure 7B displays the distribution of stalls and doubles for the individual subjects. No correlation was found between variables such as sex or age and being a "staller" or a "doubler." However, a correlation of −.58 was found between the contact duration of the finger with the pad during the no-TMS condition and the probability of a subject to be a "doubler."

Although, on average, the subjects' finger was down in time with the metronome, inaccurate tapping caused the TMS, which was locked to the metronome, to be applied also at times when the finger was not completely down. We divided the tap cycle into four parts (see Methods). Figure 4 compares the probability of a double or a stall to occur as a result of TMS perturbation at the four different stages. When calculating the probability for a particular perturbation (stall or double) to occur out of the total taps during TMS (see Table 2), a number of facts are observed. Stalls had the highest probability to occur when TMS was applied to the finger when it was completely up. On the way up, practically no stalls occur, and if an abnormality occurs there, then it is almost sure to result in a double.

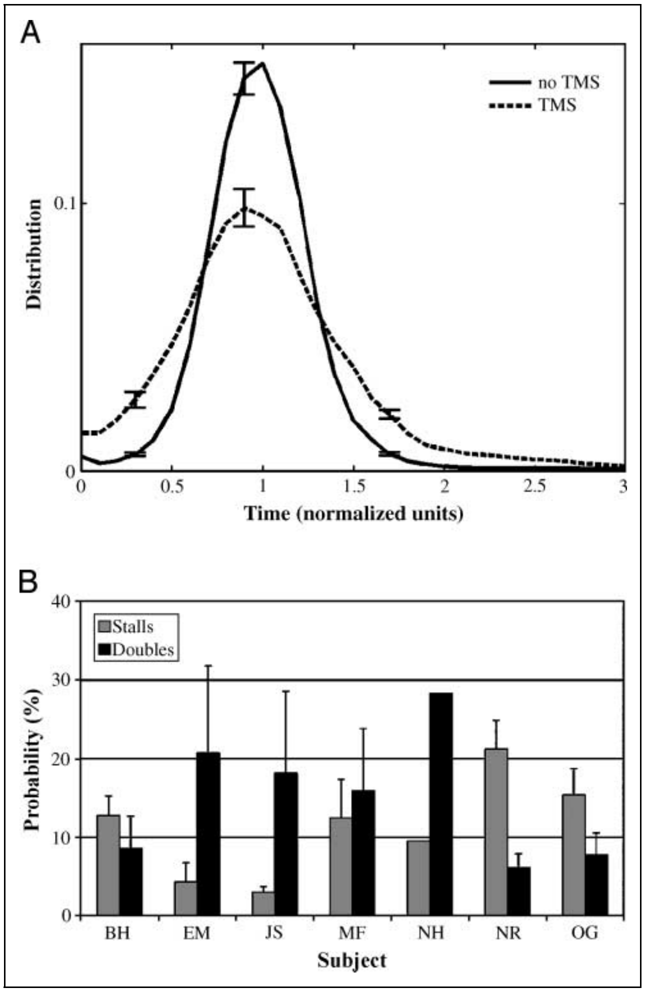

Figure 7. The possible irregularities of the finger trajectory. (A) Average distribution of the time the finger stayed down in contact with the pad, upon completion of a tap, for all taps without TMS (solid line) and all taps with TMS (broken line). The longer times indicate the existence of stalls and the shorter times the existence of doubles. Times are normalized by the average contact duration in the no-TMS condition. (B) Frequency of stalls (gray column) and doubles (black column) for all subjects. Although subjects do execute both anomalous motions, they tend to favor one of the two motions. All the subjects were right-handed. Significant correlation was found only between favored motion (double or stall) and contact duration. Subjects performed between $n = 2$ and $n = 5$ trials, except NH for whom $n = 1$.

Table 2. Division of Taps According to Where the Metronome Occurred during the Tap Cycle

	Up	*Way Down*	*Down*	*Way Up*
I. No TMS	8.3%	23.8%	66.3%	1.6%
II. TMS	7.5%	17.3%	72.0%	3.3%
IIa. Stalls	**31%**	17%	8%	3%
IIb. Doubles	16%	21%	15%	**42%**
IIc. Regulars	53%	62%	77%	55%

The first and second rows display the distribution of taps according to where the (I) metronome click (in the case of no-TMS application) or (II) the metronome click together with a TMS pulse, occurred during one of four phases of the tap cycle (see Methods). The last three rows display the probability that in Case II (during TMS) the taps were stalls, doubles, or regular taps (not stalls or doubles). In bold are the largest probabilities for stalls and doubles.

It is important to note that no significant effect of the intensity of TMS on the duration of stalls was observed. For the lowest four intensities, it was 179 (±34) msec, and for the top three intensities, it was 194 (±11) msec, although the difference between these durations is insignificant (two-tailed *t* test, $p = .64$). This contrasts with the results of Day et al. (1989) on the intensity dependence observed in delays of motion as a result of TMS.

The frequency doubling seen during TMS at 2.5 Hz also occurred at 2.0 and 3.0 Hz. At 2.0 Hz, six subjects were tested, and the mean time of the minimum in the double was at 247 (±25) msec, which is not statistically significantly different from 250 msec (two-tailed *t* test, $p = .9$), one half the period at 2.0 Hz. For the 3.0-Hz condition, three subjects were tested, and the minimum occurred at 200 (±15) msec, and here too the difference from one half the period (167 msec) is insignificant (two-tailed *t* test, $p = .16$). Four subjects were tested 3.5 Hz, in which the minimum occurred at 130 (±6) msec, insignificantly different from half the period (142.9 msec).

We did find a clear effect of frequency on the occurrence of stalls and doubles. Figure 8A displays the ratio between stalls and doubles at different frequencies for all subjects. A shift from doubles to stalls as frequency increases is observed in all subjects but one. The change can be so dramatic that a log-linear plot is required. Figure 8B displays the distribution of tap duration as a measure for stalls and doubles, for all subjects, at the lowest (2 Hz) and highest (3.5 Hz) tapping rates. Although accuracy drops with frequency, it does so both for the no-TMS and the TMS conditions. There was no significant difference for the relative change in accuracy (defined as the ratio between accuracy at TMS and accuracy at no TMS) across frequencies ($p = .2$ for difference between 2 and 2.5 Hz conditions, $p = .4$ for difference between 2.5 and 3–3.5 Hz conditions). Although experiments always started with the 2.5-Hz rate, an order effect can be ruled out because the second and third frequency conditions were randomly ordered and still the same frequency dependence was obtained across subjects. We monitored motor excitability after each condition and checked that no significant change occurred in the rMT or in the stimulation point (Pascual-Leone et al., 1998).

It was previously shown that asymmetry of flexion and extension exists in synchronized tapping and that this asymmetry may assist movement timing, especially in

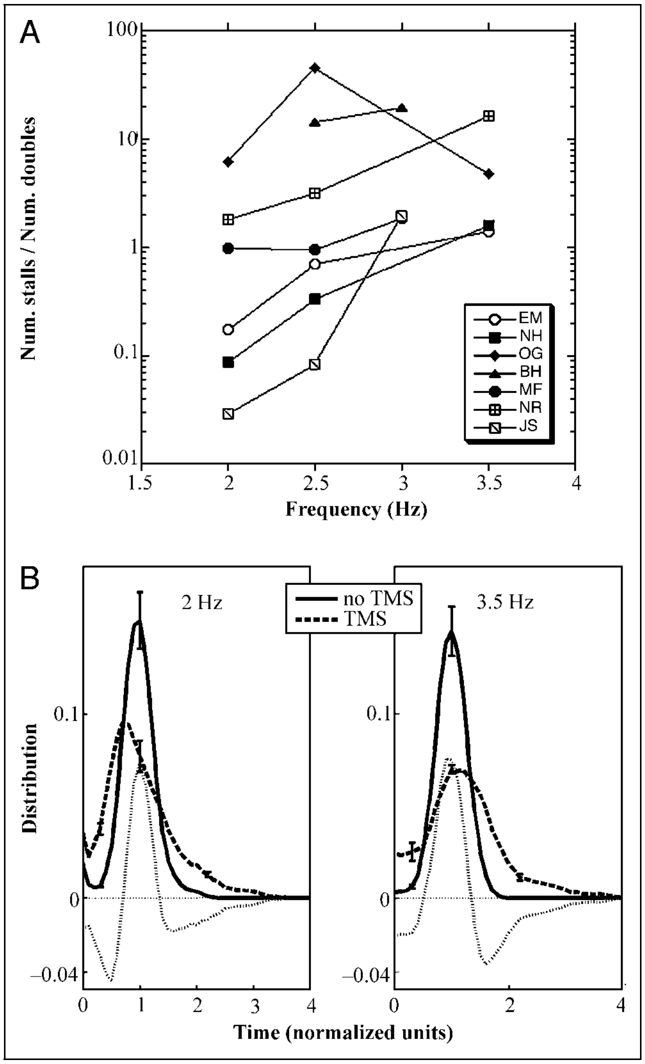

Figure 8. Frequency dependence of stalls and doubles. (A) The ratio of stalls to doubles for all the subjects in the different frequency conditions they were tested for. The increase of stalls relative to doubles was so dramatic in some cases that a log-linear axis was used. (B) Transition from stalls to doubles as measured by the average distribution of the contact duration (see Figure 7A), for the two extreme frequencies (2 Hz, right plot; 3.5 Hz, left plot). The solid line is the distribution of time the finger stayed down for all the taps without TMS, the broken line is the distribution of time for all taps with TMS. The dotted line is the difference between the solid and the broken lines. A clear shift from left to right of the dip in the difference is observed between the 2- and 3.5-Hz conditions, indicating less doubles and more stalls. Times are normalized by the average contact duration in the no TMS condition.

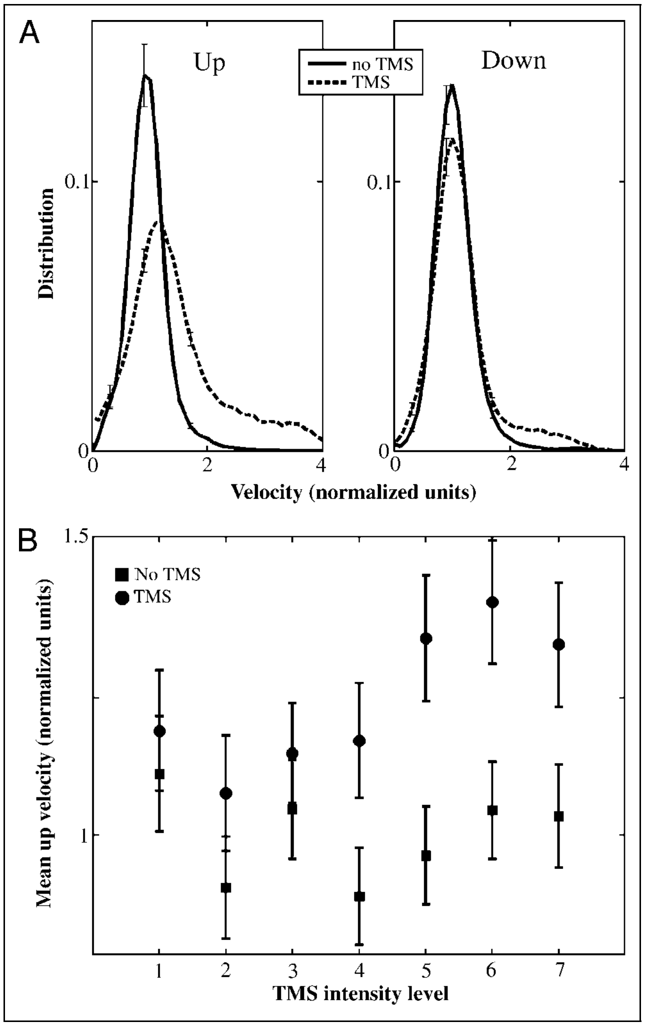

Figure 9. Effect of TMS on finger velocity. (A) Average distribution of the velocities during the up, extension motion (left) and the down, flexion motion (right) for all the taps occurring without TMS (solid line) and with TMS (broken line). Velocities were normalized by the average velocity in the no TMS condition. (B) The mean normalized up velocity as a function of the seven TMS intensity levels (see Methods). Although the actual TMS intensities varied between subjects, the seven intensity levels are a measure of the reactivity of the cortex to the TMS stimulation and are distributed around each individual's rMT. The squares represent the baseline velocity level when no TMS was applied (and therefore no dependence on intensity) and the circles represent the velocities when TMS was applied.

more difficult tapping conditions (Balasubramaniam et al., 2004). We checked whether TMS perturbations affected the relative timing between the extension and flexion phases by measuring flexion and extension average velocities (measured as ratio between the amplitude of each phase and the time). Figure 9A demonstrates the distribution of up velocities and down velocities for the no-TMS and TMS conditions for all subjects. A clear increase in the velocities of the upward moving finger during TMS is observed (Figure 9A, left panel) and is greater for the higher intensities (Figure 9B). There is no effect on the flexion phase (downward movement) (Figure 9A, right panel). This increase in the velocity of the upward movement was also observed when we analyzed separately taps that were stalls and taps that were doubles (data not shown). A randomized block design with subjects as blocks, and the extension and flexion phase velocities during no TMS or TMS as four treatments, revealed that the velocities at the extension and flexion phase were significantly different from each other in both TMS and no-TMS tapping ($p < .0001$).

A possible explanation for the existence of stalls is suggested by the report of subjects that their finger is "stuck" to the pad during stalls. To check whether the pad has a role in causing stalls, we performed a preliminary test of tapping with no pad. The data are less precise, and the absence of the sensation of touching the pad seems to detract from the ability to tap precisely. However, it soon became evident that stalls no longer occurred. In their place, we often observed an "inverse double" where the finger performed an additional half tap at the lowest part of the trajectory.

Transcranial magnetic stimulation causes a loud click when activated, which could cause sensory facilitation and could conceivably induce some of the effects we attribute to the magnetic field. Nikouline et al. (1999) showed, for example, that the click elicits auditory-evoked potentials. We therefore performed a control experiment under sham conditions, where we put a coil that was not connected to the stimulator on the head of the subject in the regular position and activated another coil that was placed just above the sham coil. This coil was activated at the same times as in the regular conditions. In this way, the subject felt the pressure of the coil on the head and heard the click coming from a very similar direction. None of the effects reported here were observed for the sham condition. This control also serves to check for the possibility of an order confound.

DISCUSSION

Our main observation is that TMS applied synchronously with the metronome induced complex finger trajectories but did not affect the timing of the tapping events. The tapping accuracy, as judged by the position of the finger at the time of the metronome click, was slightly improved by TMS at low intensities. Although this is unexpected, it is in line with recent observations of Doumas et al. (2005) that motor cortex inhibition decreased the tap–tone asynchrony (tapping inaccuracy).

The trajectory of the finger is profoundly affected by the TMS. At high intensities, large deviations from normal finger tapping occur, while the finger still manages to arrive at the pad, remarkably on time with the metronome. The deviations can be categorized into two abnormal behaviors, stalls and doubles. A consistent additional effect is the enhanced velocity of the finger on its way up.

Our measure of accuracy is different from the conventional, standard definition using the ITI. The spatial resolution of the finger trajectory supplied by our measurement apparatus enables the separation of contact times into the different phases of the finger motion and we found that TMS does not reduce the probability for the finger to be in the down phase with the metronome. The more standard measure of synchronization error also showed a slight improvement in accuracy that resulted in a slight shift of the reported negative error (Aschersleben & Prinz, 1995) toward zero.

These two observations lead us to conclude that the timekeeping and motor functions in the finger tapping task are controlled by distinct neural systems, and that the TMS applied to the primary motor cortex affects only the motor function directly. There does, however, seem to be an indirect interaction between the motor and timing circuitry (see below). Abnormal motion in response to TMS occurred randomly within a trial, indicating that the effect of TMS was limited to individual taps. This supports the assumption that continuous tapping movement is composed of multiple discrete events. This probabilistic effect of TMS on the movement trajectory is not particular for our protocol and is probably due to fluctuations in the excitability levels in the cortex.

The observed changes in trajectory cannot be attributed simply to muscular effects because deviations in the movement occur as much as 100 msec after application of the TMS. In comparison, the direct muscular response measured by EMG when TMS is applied at rest occurs within about 50 msec. The effect of the TMS was never apparent before the ongoing motion—either flexion or extension—was completed. This is in line with previous measurements (Verstynen et al., 2006; Day et al., 1989) and strengthens our conclusion that we are affecting directly the motor plan rather than the motor execution.

The dependence of the number of stalls on frequency may be related to the asymmetry between the upward and downward phases of the trajectory. The probability for getting a stall was highest if the TMS was delivered when the finger was fully extended or on the way down, whereas it rarely occurred if the finger was on the way up. Coupled with the decrease we measure in relative time spent on the way up as the frequency increases, this may explain the change in relative occurrences of doubles and stalls.

Although stalls and doubles look very different, we attribute them to the same basic mechanism. We understand the stall to be caused by the presence of the pad, and in its absence would expect an exaggerated flexion, perhaps coupled to an inverse double. Explaining the precise motion created by the TMS in conjunction with tapping, using mathematical models and simulations, is beyond the scope of the current article, and is being addressed separately.

A recent article (Verstynen et al., 2006) employed a complementary approach to evaluate the relative contributions of the primary motor cortex in response timing and execution. Their protocol involved an unpaced tapping paradigm, during which the TMS pulses were applied at random times, independent of the subjects' responses. The measurement apparatus employed in their study was a telegraph-style response key. They find a similar intensity-dependent global increase in ITI variability, regardless of its timing with respect to the TMS pulse. This is attributed to noise that is added on to the implementation, and this is similar to our findings on the higher variability in ITI under TMS, which we attribute to deviations in timing caused by complex finger trajectories under TMS.

Verstynen et al. report a delay in the tap defining the end of the interval that occurs when the TMS is applied during a critical time window of 100 msec just prior to the flexion onset. This corresponds to TMS occurring during what we term Phase 3 of the trajectory (finger completely up). In this case, stalls are most probable to occur. It would be interesting to see whether in the full spatial trajectories of the Verstynen experiment, stall-like behavior occurs. Note that in our experiments the stalls do not cause deviations of the mean ITI. This is probably because of our metronome-paced tapping paradigm.

The paced versus unpaced paradigms also impact on long-term effects. In our case, the next metronome beat and its associated TMS pulse reset the timing and cut off any long-term correlations and any changes in ITI caused by delays of the motion. This is very different in the unpaced results reported by Verstynen et al. (2006).

Delay of execution of voluntary motion by TMS, reminiscent to the stalls we observed, has been previously described (Verstynen et al., 2006; Haggard & Magno, 1999; Berardelli et al., 1994; Pascual-Leone, Brasil-Neto, et al., 1992; Pascual-Leone, Valls-Sole, et al., 1992; Day et al., 1989). We view the stalls and observed delays as different. First, in the absence of a pad, we observed no obvious stalls. Second, the delay interval in previous experiments is intensity dependent, whereas we observed constant stall intervals. Third, the duration of the motion following the delay was unchanged in previous experiments, whereas in our experiment it was speeded up. It is plausible that the absence of delays in our experiment is related to the ongoing nature of the task, without stop-and-go triggering.

Day et al. (1989) showed that it is possible to selectively delay the two independent phases of the motion (agonist and antagonist). It is possible that, in our case, the stalls are a kind of mistiming between the two phases, which in the absence of a pad would lead to different motions.

The main candidate in the brain for the timekeeping function during tapping is the cerebellum (Spencer et al., 2003; Ivry, Spencer, Zelaznik, & Diedrichsen, 2002). A primary pathway from the cerebellum to the motor cortex is known to exist (Middleton & Strick, 1994; Strick, Hoover, & Mushiake, 1993). However, our attempts to target the cerebellum with TMS, following the protocol of Theoret, Haque, and Pascual-Leone (2001), and thereby to cause change in the timekeeping, were not successful. Although this could indicate that the timing circuitry is located elsewhere, due to the depth of the cerebellum, we are unable to exclude the possibility that TMS was not effective enough (Jäncke, Steinmetz, Benilow, & Ziemann, 2004) and, in practice, a virtual lesion was not created there.

Spencer et al. (2005) showed that lesions in the cerebellum lead to impaired timing control of tapping. Interestingly, the appearance of doubles is also reported in that article, where both normal subjects and cerebellar patients occasionally executed an additional tap within the time frame of a single tap. The probability of a lesioned patient to perform a double was greater by about a factor of 3. These authors suggest that the doubles may reflect a release of inhibition of planned movements. Doubles also appear in the data of Meyer and Voss (2000) for tapping with TMS, although their existence is not addressed directly.

We therefore conclude that the appearance of doubles in our case indicates that we do influence the timekeeper, albeit by an indirect interaction with the motor function. The involvement of the timekeeper is strengthened by the precise halving of the period that we observe in both stalls and doubles.

The observed intersubject variation in the distribution of stalls and doubles may be related to the different tapping patterns employed by the different subjects. Semjen and Summers (2002) found that varying the contact duration of movement affected trajectories, but not timing or accuracy. We similarly find a correlation between duration of contact with the pad and the probability for a subject to be a "staller" or a "doubler." It may also be that the cognitive strategy adopted by the subjects to resist the TMS-induced perturbations (Bonnard, Camus, de Graaf, & Pailhous, 2003) accounts for this intersubject variability, although it is probably not the only explanation. It is also possible that different accentuation patterns (Sternad & Corcos, 2001) may affect the distribution of stalls and doubles across subjects. This remains to be investigated in future experiments.

A persistent result we obtained is the speeding up of the finger on its motion upward for taps occurring during TMS, both in the presence of stalls and doubles and in their absence. If the TMS causes delayed antagonist activation, then the agonist motion would be unhindered, and thus, naturally faster. Mechanical perturbation can also lead to speeding up of the finger (Kay et al., 1991), but the major effect there was a change in tapping phase.

The downward motion, on the other hand, is toward the temporal goal controlled by the metronome beat (Balasubramaniam et al., 2004), and therefore, under control of the timekeeping mechanism. That explains why the downward motion is naturally faster (Balasubramaniam et al., 2004). This can also explain why the downward motion is not affected by the TMS.

It is possible that a generalized motor plan exists for the tapping motion where a representation of the sequence of events in a tap and the relative timing between them is kept (Vorberg & Wing, 1996). Upon transformation from intention to action, an explicit temporal goal is set by a timer (e.g., the cerebellum; Spencer et al., 2003) and the exact performance is then controlled by parameters that satisfy the various temporal, mechanical, and dynamical constraints of the motion (Hogan, Bizzi, Mussa-Ivaldi, & Flash, 1987). The TMS perturbation can interfere in this process by releasing the plan into activation mode earlier than intended. This would require an adjustment of the temporal parameters in order to carry out the planned sequence of extension–flexion motions and obtain the initial goal, resulting in a multiple activation of this sequence, in our case, a double tap.

Because the representation of the motor plan needs to be continuous to account for the repetitive nature of the motion, it may be that the order of sequence events (i.e., first extension and then flexion) is flexible and can be inverted. In this case, when the plan is released earlier than intended by the TMS perturbation, an inverted double tap can also occur, accounting for the inverted doubling we presume is happening in the case of the stalls.

Subjects were generally unaware of the precise change in the trajectory, even when performing an additional tapping step. This suggests that fast error corrections to the motor function are automatic, occur outside of M1 (Doumas et al., 2005), and do not enter into awareness. On the other hand, the subjects were well aware of the precision with which they were tapping (i.e., of the timekeeper function). It follows that timekeeping is a higher-level function then the motor program.

The possibility that TMS causes an external activation of the motor command prior to the intended time is further supported by previous observations of an effect of a startle on the speeding up of movement execution (Sanegre, Castellote, Haggard, & Valls-Sole, 2004). When a startling auditory stimulus is applied at the same time as the imperative signal in a simple reaction time task experiment, movement execution is speeded up (Valls-Sole, Rothwell, Goulart, Cossu, & Munoz, 1999). In this case, it is hypothesized that the effect of startle on reaction time is due to external activation of the whole set of motor commands prepared for the intended movement, either via subcortical pathways or by intersensory facilitation (Pascual-Leone, Brasil-Neto, et al., 1992; Pascual-Leone, Valls-Sole, et al., 1992).

An intriguing fact is that both abnormal trajectories occur in precisely one half of the period set by the timekeeper, effectively doubling the frequency. It is interesting to note, in this context, that the phenomenon of frequency doubling is known to occur in certain nonlinear dynamical systems. The motor and timekeeping functions must interact because the timekeeper must adapt to correct for the changes set by the motor dysfunction, and the resultant motion combines input from both these neural systems. The appearance of higher harmonics, as in frequency doubling, may be an indication of an interaction involving nonlinear terms between the oscillator governing the finger tapping and the periodic forcing of the TMS.

The question remains: What is the precise form of the interaction that causes trajectory deviations at exactly double the requested frequency and not other combinations? Frequency doubling phenomenon can appear in oscillating systems when perturbed mechanically by an external force. Thus, we suggest that the explanation lies in the nonlinear interaction of the muscular system involved in the oscillatory motion with the external TMS perturbation. However, the exact formulation of this interaction is beyond the scope of this article.

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