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Theta Burst Stimulation of the Human Motor Cortex

Report

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Summary

It has been 30 years since the discovery that repeated electrical stimulation of neural pathways can lead to long-term potentiation in hippocampal slices. With its relevance to processes such as learning and memory, the technique has produced a vast literature on mechanisms of synaptic plasticity in animal models. To date, the most promising method for transferring these methods to humans is repetitive transcranial magnetic stimulation (rTMS), a noninvasive method of stimulating neural pathways in the brain of conscious subjects through the intact scalp. However, effects on synaptic plasticity reported are often weak, highly variable between individuals, and rarely last longer than 30 min. Here we describe a very rapid method of conditioning the human motor cortex using rTMS that produces a controllable, consistent, long-lasting, and powerful effect on motor cortex physiology and behavior after an application period of only 20–190 s.

Introduction

In animal experiments, it has long been possible to probe and manipulate the efficacy of synaptic transmission by repetitive electrical stimulation of central nervous pathways. This leads to the well-studied phenomena of long-term potentiation (LTP) and depression (LTD) of synaptic connections. Repetitive transcranial magnetic stimulation (rTMS), which is a noninvasive method of stimulating the brain of conscious human subjects through the intact scalp, has obvious potential for mimicking the effects that have been observed in animal models. Yet despite the striking effects on synaptic transmission that have been achieved in animals, translation to the human brain using rTMS has been relatively disappointing.

Investigations have been carried out on three levels: physiological, behavioral, and clinical. All are designed to detect changes in function that outlast the application of particular patterns of rTMS to selected areas of cortex. The majority of physiological studies have employed the motor cortex since it is possible to use the size of the electromyographic (EMG) response to a single TMS pulse as an objective measure of cortical excitability. Here, results are often weak, highly variable from one individual to another (Maeda et al., 2000), and rarely last longer than half an hour. Behaviorally, the experiments on the motor system produce no obvious effects on basic motor parameters such as strength or speed of contraction (Muellbacher et al., 2000). However, small changes can be seen in more complex paradigms. Similarly, rTMS over other cortical areas can induce subtle changes in cognitive functions (Evers et al., 2001; Hadland et al., 2001; Sparing et al., 2001), but again these are relatively modest. Clinically, rTMS has been used to try to treat a variety of neurological and psychiatric conditions from Parkinson's disease to obsessive-compulsive disorder. The largest number of trials has been for depression, but again, the results have been equivocal (Hausmann et al., 2004; Martin et al., 2003).

There are several possible reasons for the previous disappointing results of rTMS: first, even in animal experiments, LTP/LTD is difficult to demonstrate in the cortex of awake and freely moving animals without the use of extended or repeated sessions of stimulation (Froc et al., 2000; Trepel and Racine, 1998). Second, concerns over safety have limited many human studies to relatively low frequencies of stimulation (usually $<$10 Hz) (Wassermann, 1998), whereas animal studies often use much higher frequencies such as the "theta burst" paradigm (3–5 pulses at 100 Hz repeated at 5 Hz) (Hess et al., 1996; Huemmeke et al., 2002; Larson and Lynch, 1986; Vickery et al., 1997). Third, TMS in humans is relatively nonfocal, and therefore cannot be used to target spatially specific neural connections. In most instances, this means that rTMS will activate a mixture of systems that potentially could have interacting effects that make the final outcome difficult to predict.

Other stimulation methods have been used to try to induce plastic changes in human cortex, for example paired associative stimulation (PAS) (Ridding and Uy, 2003; Stefan et al., 2000) or transcranial direct current stimulation (Nitsche and Paulus, 2000). PAS can produce controllable change in cortical excitability, but protocols typically require periods of conditioning of around 30 min, and peripheral stimulation is given at 2–3 times sensory threshold, which may be uncomfortable for some subjects. There is less experience with the use of tDCS, and again conditioning times of more than several minutes typically are needed to produce any effect.

A recent pilot study has shown that a single short, low-intensity burst of rTMS at 50 Hz is safe and can target specific populations of neurons in the motor cortex (Huang and Rothwell, 2004). In the present experiments, we have aimed to produce clear after effects of rTMS in the human motor cortex by employing repeated application of such bursts in modified "theta burst" paradigms (TBS).

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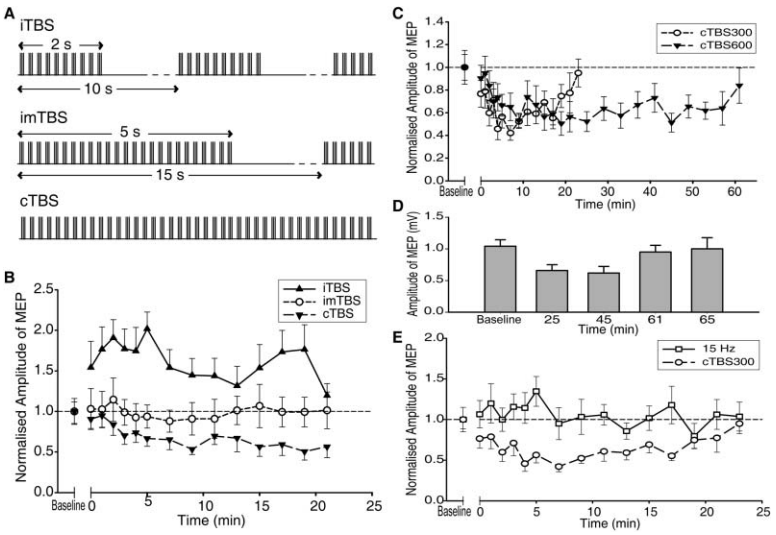

Figure 1. Paradigms of TBS and Their Effects on MEPs

(A) Graphical illustration of the three stimulation paradigms used. Each paradigm uses a theta burst stimulation pattern (TBS) in which 3 pulses of stimulation are given at 50 Hz, repeated every 200 ms. In the intermittent theta burst stimulation pattern (iTBS), a 2 s train of TBS is repeated every 10 s for a total of 190 s (600 pulses). In the intermediate theta burst stimulation paradigm (imTBS), a 5 s train of TBS is repeated every 15 s for a total of 110 s (600 pulses). In the continuous theta burst stimulation paradigm (cTBS), a 40 s train of uninterrupted TBS is given (600 pulses).

(B) Time course of changes in MEP amplitude following conditioning with iTBS (closed up triangle), cTBS (closed down triangle), or imTBS (open circle). There was a significant effect of pattern of stimulation on change in MEP size following stimulation [$F(2,16) = 20.32$, $p < 0.001$], with significant post hoc differences between each pattern of stimulation. There was a significant facilitation of MEP size following iTBS lasting for about 15 min, and a significant reduction of MEP size following cTBS lasting for nearly 60 min. imTBS produced no significant changes in MEP size.

(C) Comparison of the effects of cTBS given for 20 s (300 pulses; cTBS300 [open circle]) with the same paradigm given for 40 s (600 pulses; cTBS600 [closed down triangle]). There was a significant effect of duration of cTBS conditioning on the time course of the effect (significant TIME $\times$ DURATION interaction [$F(14,112) = 2.24$, $p < 0.05$]) with the effect of cTBS300 lasting about 20 min compared to the effect of cTBS600, which lasted about 60 min.

(D) Effects of cTBS600 on a longer timescale in order to confirm the return to baseline levels after 1 hr. Data are from 6 subjects and show suppression at 25 and 45 min but no effect at 61 and 65 min.

(E) Comparison of the effect of continuous 15 Hz stimulation for 20 s (open square) (300 pulses) with cTBS given for 20 s (open circle) (300 pulses). Only the cTBS paradigm had any effect on MEP size following stimulation, and there was a significant interaction between TIME and PATTERN [$F(14,84) = 2.55$, $p < 0.005$]. This graph also shows more clearly than (C) that the effect of cTBS300 had returned to baseline by 20 min.

Results and Discussion

In the first experiment, three patterns of TBS (Figure 1A), each consisting of a total of 600 pulses at an intensity of 80% active motor threshold, were given on different days to the primary motor cortex of the same group of subjects. The basic element of all of these patterns was a burst of 3 stimuli at 50 Hz (i.e., 20 ms between each stimulus), which was repeated at intervals of 200 ms (i.e., 5 Hz). We refer to these patterns as continuous TBS (cTBS), intermittent TBS (iTBS), and intermediate TBS (imTBS). The excitability of the corticospinal system before and after TBS was measured using single pulse TMS to evoke EMG responses (motor evoked potentials, MEPs) in a small hand muscle. Figure 1B shows that after cTBS, MEPs were suppressed for more than 20 min, whereas they were unaffected after imTBS and facilitated after iTBS (ANOVA: significant effect of PATTERN [i.e., iTBS, imTBS, or cTBS] [$F(2,16) = 20.32$, $p < 0.001$] with significant post hoc differences between each pair of TBS patterns). Figure 1C shows that the duration of the after effects was shorter when fewer TMS pulses were applied in the cTBS pattern. MEPs were suppressed for 60 min after a total of 600 pulses (i.e., 40 s cTBS), whereas they were suppressed for only 20 min after 300 pulses (i.e., 20 s cTBS) (ANOVA: significant TIME $\times$ DURATION interaction [$F(14,112) = 2.24$, $p < 0.05$]). In a subset of 6 subjects, we extended the period of measurement beyond 60 min in order to confirm that the effects of 40 s cTBS had returned to baseline after 1 hr (Figure 1D). The one-way ANOVA on this data revealed a significant effect to TIME [$F(3,15) = 4.36$, $p < 0.05$], with post hoc tests showing significant suppression of MEPs at 25 and 45 min but not at 61 and 65 min.

In order to understand which features of TBS patterns are critical to the observed after effects, we compared the results of applying 300 TMS pulses continuously at 15 Hz with the same number of pulses in the cTBS pattern. Although it took 20 s to apply each type of conditioning, only the cTBS pattern had any after effect on the responses to TMS (Figure 1E) (significant interaction between TIME and PATTERN [$F(14,84) = 2.55$, $p < 0.005$]), confirming the importance of the high-frequency burst component of TBS for producing long-lasting after effects.

A second experiment compared the effect of applying a single train of TBS for either 2 s (i.e., the individual component of the iTBS pattern) or 5 s (the component of the imTBS pattern). Figure 2A shows that as expected from the small total number of pulses applied, these short trains produced after effects that lasted only 15 s or so. However, a 2 s train had a purely facilitatory effect on MEPs (Figure 2A), whereas MEPs were initially facilitated after a 5 s train, but then suppressed at 10 s before returning to baseline at 15 s (Figure 2B). Given that a 20 s train of TBS (i.e., the cTBS pattern) is purely suppressive, this suggests that a single train of TBS can lead to a mixture of suppressive and facilitatory effects on MEPs, with facilitation building up faster than suppression, but with suppression being more powerful in the long term.

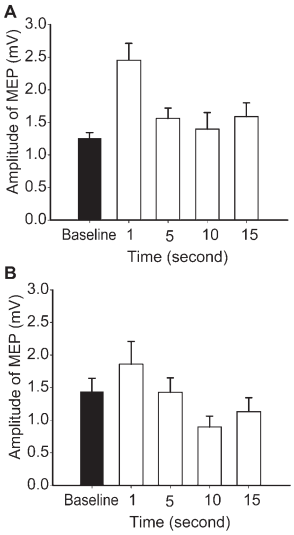

Figure 2. The Effect on MEP Size of a Short Burst of TBS

MEP size was measured at baseline and then at 1, 5, 10, and 15 s following the end of stimulation. Following a 2 s train of TBS (A), there was a significant facilitation of MEP size [$F(4,16) = 6.99$, $p < 0.005$]. In contrast, a 5 s train of TBS (B) produced an initial significant facilitation of MEP size at 1 s after the end of stimulation ($p < 0.05$) followed by a significant suppression of MEP size at 10 s ($p < 0.05$).

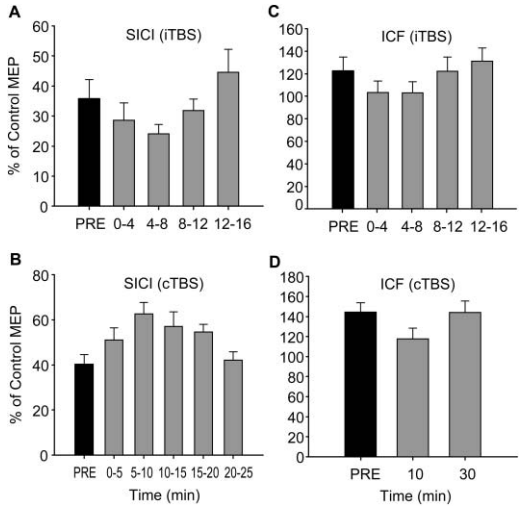

Figure 3. The Effect of iTBS and cTBS on Short Intracortical Inhibition and Facilitation

(A and B) SICI was significantly increased (A) following iTBS [$F(4,24) = 5.01$, $p < 0.005$], but was reduced (B) following cTBS [$F(5,30) = 3.75$, $p < 0.01$].

(C and D) ICF was not significantly altered (C) following iTBS, but was significantly reduced (D) at 10 min following cTBS [$F(2,12) = 7.40$, $p < 0.01$].

Given the very low intensity of the individual pulses used in the conditioning trains (80% AMT), it is unlikely that TBS produced any activity in descending corticospinal fibers, and therefore that there were any direct effects of TBS on the excitability of circuits in the spinal cord that could contribute to the MEP changes that were observed. Consistent with this, we found that cTBS with 300 pulses had no effect on H reflexes evoked in forearm flexor muscles whereas MEPs were suppressed (ANOVA on log-transformed amplitude data of H-reflex and MEP: significant interaction between TIME and RESPONSE TYPE [$F(1,7) = 6.05$, $p < 0.05$]).

To confirm that TBS has an effect on the excitability of circuits intrinsic to the motor cortex, we measured short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) before and after iTBS and cTBS300 using a paired pulse paradigm. In these experiments, the intensity of the second, test, stimulus was adjusted so that it evoked the same size of baseline MEP before and after TBS. Figures 3A and 3B shows that SICI was significantly facilitated following iTBS (ANOVA on the time course: [$F(4,24) = 5.01$, $p < 0.005$]) and suppressed after cTBS [$F(5,30) = 3.75$, $p < 0.01$]. In contrast, ICF was unaffected by iTBS and slightly reduced 10 min after cTBS300 [$F(2,12) = 7.40$, $p < 0.01$] (Figures 3C and 3D).

Unlike most other methods of conditioning the motor cortex (Chen et al., 1997; Muellbacher et al., 2000), cTBS with 300 pulses in total produced clear changes in simple reaction times. In this experiment, cTBS300 was applied to the left motor cortex and reaction times measured in the right (conditioned) and left (unconditioned) hands (Figure 4). A two-factor ANOVA revealed a significant interaction between time (before and after cTBS300) and hand [$F(2,16) = 4.30$, $p < 0.05$], indicating that cTBS300 had a different effect on the reaction times of the two hands. One-factor analyses showed that there was a significant effect of time in both hands (conditioned hand: [$F(2,16) = 12.77$, $p < 0.001$]; unconditioned hand: [$F(2,16) = 7.82$, $p < 0.005$]). However, in the unconditioned hand this was due to a decrease in reaction times 30 min after cTBS300, whereas in the conditioned hand it was due to an increase in reaction time 10 min after cTBS300. The accuracy of the force with which subjects pressed the button was not changed in either hand following conditioning (conditioned hand: [$F(2,16) = 0.18$, ns]; unconditioned hand: [$F(2,16) = 1.14$, ns]).

These data confirm that very short periods of low-intensity TBS over motor cortex can have powerful effects on physiology and behavior that outlast the conditioning by up to 1 hr. Since spinal H-reflexes were unaffected whereas two sets of intracortical circuitry tested by SICI (a probable GABAa-ergic pathway [Chen et al., 1998;

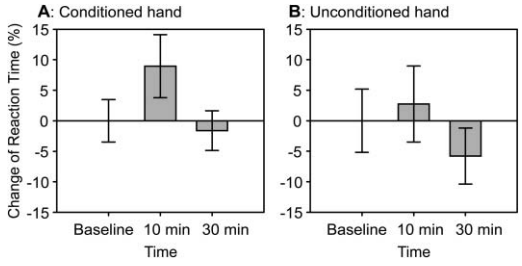

Figure 4. Changes in Simple Reaction Time following cTBS

There was a significant lengthening of reaction time in the conditioned hand 10 min (A) after cTBS [$F(2,16) = 4.30$, $p < 0.05$] and a significant shortening of reaction time in the unconditioned hand 30 min (B) after cTBS [$F(2,16) = 7.82$, $p < 0.005$].

Hanajima et al., 1998; Reis et al., 2002; Ziemann et al., 1998]) and ICF (pathway unknown) were clearly modulated, it seems likely that TBS was exerting its main effects on the excitability of neurons in the motor cortex. Given that there is now good evidence that other forms of TMS conditioning produce their after effects by changing the effectiveness of synaptic interactions (Lee et al., 2003; Siebner et al., 2000, 2003), we believe that the present results are compatible with induction of similar mechanisms.

At first sight, the opposite effects of different patterns of TBS are surprising. However, a similar dissociation has been noted in previous work on animal preparations: patterns of intermittent TBS similar to our iTBS paradigm are routinely used to facilitate synaptic connections (Capocchi et al., 1992; Hess and Donoghue, 1996; Heynen and Bear, 2001), whereas a small number of studies have used longer trains of TBS-like paradigms to produce suppression (Heusler et al., 2000; Takita et al., 1999). Our data would be compatible with similar mechanisms in which cTBS might reduce the efficacy of transmission through the synaptic connections that are recruited when evoking an MEP (i.e., the I wave circuits), whereas iTBS would have the opposite effect. Similar arguments can account for the changes in SICI and ICF that we observed. Thus, we suggest that cTBS decreased the effectiveness of synaptic connections that are recruited in circuits involved in both SICI and ICF. This would reduce SICI, resulting in less MEP inhibition probed by SICI, and also reduce MEP facilitation probed with ICF. Conversely, iTBS, which facilitated MEPs, might also increase the effectiveness of connections involved in SICI and increase MEP suppression probed by SICI. There was no corresponding facilitation of the SICF circuit in the present data after iTBS. The reason for this is unclear, but it may be related to the fact that more than one circuit contributes to ICF (Hanajima et al., 1998) or that we simply did not have sufficient subjects to demonstrate statistically significant facilitation. If so, then a simplified conclusion would be that cTBS had an inhibitory effect on the circuits underlying MEP production (I wave circuits), SICI, and ICF, while iTBS had an opposite effect on these circuits.

We found our different TBS paradigms to have large effect sizes and acceptable interindividual variability compared with traditional rTMS paradigms. Thus, the mean percentage change of MEP size in the period where the maximum effect occurred (i.e., 7–14 min after cTBS300, 15–40 min after cTBS600, 1–10 min after iTBS) was −45.0% (SD = 8.9%), −42.2% (SD = 24.0%), and 75.7% (SD = 40.9%), respectively. These effect sizes and variability compare well with traditional rTMS paradigms, such as those explored by Maeda et al. (2000), where a much larger number of rTMS pulses (1600) produced mean effects of −34.03% (SD = 37.87%) after 1 Hz and 37.87% (SD = 53.59%) after 10 Hz.

The effectiveness of these paradigms raises ethical issues about the use of these methods in normal human subjects, who have nothing to gain from modulation of synaptic plasticity, in contrast to patients with particular neurological disorders. We were aware of these ethical issues, so in addition to putting our proposed experimental methods before the ethics committee of our institution and gaining consent from subjects, we pursued the experiments in an incremental fashion starting with smaller intensities and lower frequencies of stimulation than those reported here. We found in all experiments that cortical excitability eventually returned to baseline, and no subject reported any side effects from experimentation. However, as methods for inducing plastic changes in human cortex become more powerful, such issues will require constant scrutiny and vigilance on the part of experimenters.

The results of the experiments with single trains of TBS suggest that in humans, TBS produces a mixture of facilitatory and inhibitory effects on synaptic transmission, with facilitation building up faster than inhibition. If we assume that both facilitation and inhibition saturate at some level, then it is possible to explain the main features of the results as long as we allow inhibition to dominate in the long run. Thus, a short, intermittent protocol such as iTBS would favor rapid build-up of facilitation. In contrast, a longer lasting continuous protocol such as cTBS would initially produce facilitation, but eventually this would saturate, and inhibitory effects (which build up slower but saturate at a higher level) would dominate. An intermediate protocol such as imTBS might have no net effect by achieving a balance between the build-up of inhibitory and facilitatory effects. This model is speculative at this stage but would be consistent with several studies in animal preparations in which a mixture of opposing effects on LTP and LTD has been induced by the same protocol. For example, blocking some of the pathways that are needed for LTD induction, e.g., inositol triphosphate receptors (Nishiyama et al., 2000), can result in LTP after a protocol that usually produces LTD, whereas blocking LTP-dependent receptors, e.g., NMDA subunit 2A (Liu et al., 2004), may convert LTP into LTD. In addition, it has been shown that on occasion, a single protocol can cause LTP in some neurons, whereas it results in LTD in others (Hirsch and Crepel, 1990; Shen et al., 2003).

In conclusion, we have developed novel methods of delivering rTMS based on patterns of theta burst stimulation. We have found these stimulation paradigms to be safe in normal subjects and capable of producing consistent, rapid, and controllable electrophysiological and behavioral changes in the function of the human motor system that outlast the period of stimulation by more than 60 min. In particular, we have found that the pattern of delivery of TBS (continuous versus intermittent) is crucial in determining the direction of change in synaptic efficiency. The method may prove useful not only in the motor cortex but also in other regions of the brain for both the study of normal human physiology and for therapeutic manipulation of brain plasticity.

Experimental Procedures

Subjects

Subjects were nine healthy volunteers between the ages of 23 and 52 (mean age: 33.6 ± 7.8 years) who gave their informed consent for the experiments. The project protocol was approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery.

Stimulation and Recording

Subjects were seated and EMGs recorded with a gain of 1000 and 5000 using Ag-AgCl surface electrodes over the right first dorsal

interosseous muscle (dominant hand in all subjects). Magnetic stimulation was given over the hand area of the motor cortex using a hand-held figure of eight coil (70 mm standard coil, Magstim Co., Whitland, Dyfed, UK) placed tangentially to the scalp with the handle pointing posteriorly. Single and paired pulses were delivered by Magstim 200 machines, and rTMS was delivered using a Magstim Super Rapid stimulator. The stimulation intensity was defined in relation to the active motor threshold (AMT) for each Magstim machine separately as the minimum single pulse intensity required to produce an MEP of greater than 200 μV on more than five out of ten trials from the contralateral FDI while the subject was maintaining a voluntary contraction of about 20% of maximum using visual feedback.

Experiments

The patterns of rTMS all consisted of bursts containing 3 pulses at 50 Hz and an intensity of 80% AMT repeated at 200 ms intervals (i.e., at 5 Hz). In the intermittent theta burst stimulation pattern (iTBS), a 2 s train of TBS is repeated every 10 s for a total of 190 s (600 pulses). In the intermediate theta burst stimulation paradigm (imTBS), a 5 s train of TBS is repeated every 15 s for a total of 110 s (600 pulses). In the continuous theta burst stimulation paradigm (cTBS), a 40 s train of uninterrupted TBS is given (600 pulses) (Figure 1A). An additional comparison was made in some subjects with regular 15 Hz stimulation at the same intensity.

Corticospinal excitability was assessed by measuring the peak-to-peak amplitude of MEPs in the contralateral FDI muscle to single pulse TMS in resting subjects. Before TBS, 30 pulses were given every 4.5–5.5 s. After TBS, batches of MEPs to 12 single pulses were measured at different intervals.

To better understand the mechanism of our different TBS paradigms, we explored the effect of a single train of 10 and 25 bursts given over the motor hand area. MEPs were accessed 4–5 s before the train of bursts and at 1 s, 5 s, 10 s, and 15 s after the train in one block of testing. The block was then repeated every 40–45 s for 10 repeats. Two separate sessions using either a 10 burst or a 25 burst train were assessed in each subject. Five subjects (3 men, 2 women; mean age, 27 $\pm$ 5 years) were recruited in this part.

We assessed short interval intracortical inhibition (SICI) and facilitation (ICF) in the motor hand area of seven subjects before and after TBS using the double-pulse method described by Kujirai et al. (1993). SICI was evaluated at an interstimulus interval (ISI) of 2 ms using a conditioning intensity of 80% AMT, and ICF at an ISI of 10 ms with a conditioning intensity of 90% AMT. Two blocks of baseline SICI and ICF were recorded with 10 trials of each condition randomly intermixed with controls. The RMT was increased from 49.0% $\pm$ 8.9% to 51.0% $\pm$ 9.7% of maximum output of the magnetic stimulator ($t = -3.24$, $p < 0.05$) by cTBS, while AMT stayed unchanged ($t = 0.55$, ns). We therefore adjusted the intensity of the test stimuli while assessing SICI and ICF after TBS to maintain the amplitude of test MEPs at approximately 1 mV, but left the conditioning intensity unchanged.

We also tested the H-reflex and MEP in the contralateral flexor carpi radialis (FCR) muscle before and after cTBS on seven subjects. One block mixing 12 trials of H-reflex and 12 trials of MEP was recorded prior to conditioning, and another block was recorded at 10 min after cTBS.

In a separate experiment, we assessed reaction time before and after cTBS in nine subjects. Subjects were seated in a comfortable chair with each index finger placed on a button. An electrical stimulus at an intensity of 3 times sensory threshold was delivered randomly to the left or the right hand through Ag/Ag-Cl electrodes attached over the hypothenar eminence. Subjects were instructed that when they felt a stimulus on the right or the left hand, they were to press the button under the corresponding finger as quickly as possible. In addition, subjects were asked to press the button with a particular force (approximately 2.5 N) with respect to visual feedback given on a screen in front of them.

Two blocks of reaction time testing were performed, with 40 stimuli to each hand given at random intervals, ranging from 1.5 to 2.5 s, and in a random pattern. cTBS was then given over the left motor hand area, and the process was repeated at 10 and 30 min.

Data Analysis

Data were analyzed using SPSS for Windows version 11.0. Repeated measures ANOVA was used to compare variables before and after TBS, and paired t tests were used to compare the effect of TBS on H-reflexes and MEPs recorded from FCR and the effect of a single pulse. Statistics for the data in Figure 1 comparing the effect of iTBS, imTBS, and cTBS were performed on normalized data, whereas the statistical analysis of each time course separately was performed on absolute values. The comparison of data between MEP and H-reflex was performed on log-transformed values in order to normalize the distribution of the amplitude data. All figures represent group data. Error bars refer to the standard error of the measurements.

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