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The theoretical model of theta burst form of repetitive transcranial magnetic stimulation

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Abstract

Objective—Theta burst stimulation, a form of repetitive transcranial magnetic stimulation, can induce lasting changes in corticospinal excitability that are thought to involve long-term potentiation/depression (LTP/LTD)-like effects on cortical synapses. The pattern of delivery of TBS is crucial in determining the direction of change in synaptic efficiency. Previously we explained this by postulating (1) that a single burst of stimulation induces a mixture of excitatory and inhibitory effects and (2) those effects may cascade to produce long-lasting effects. Here we formalise those ideas into a simple mathematical model.

Methods—The model is based on a simplified description of the glutamatergic synapse in which postsynaptic Ca^{2+} entry initiates processes leading to different amount of potentiation and depression of synaptic transmission. The final effect on the synapse results from summation of the two effects.

Results—The model using these assumptions can fit reported data. Metaplastic effects of voluntary contraction on the response to TBS can be incorporated by changing time constants in the model.

Conclusions—The pattern-dependent after-effects and interactions with voluntary contraction can be successfully modelled by using reasonable assumptions about known cellular mechanisms of plasticity.

Significance—The model could provide insight into development of new plasticity induction protocols using TMS.

Keywords

theta burst stimulation; TBS; rTMS; model; plasticity; long-term potentiation; long-term depression

INTRODUCTION

Repeated electrical stimulation of neural circuits in the brains of animal preparations can alter the efficiency of synaptic transmission and lead to synaptic long-term potentiation (LTP) or long-term depression (LTD), which in turn are thought to be closely linked to

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Supplementary material legend: TBS theoretical model. The program is built around the MATLAB language.

processes of learning, memory and functional cortical reorganisation in response to injury (Hess and Donoghue, 1994). In the past 10-15 years, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (TDCS) have emerged as potential methods for causing similar changes in the cerebral cortex of conscious humans (Muellbacher et al., 2000; Siebner and Rothwell, 2003; Ziemann, 2004). In general, as in animal studies using direct electrical stimulation of cortex, experiments using rTMS over the motor cortex have suggested that the frequency of stimulation is the most important determinant of the direction of the after effects. Thus, low frequency (1 Hz) stimulation tends to reduce corticospinal excitability (i.e. an LTD-like effect) whereas higher frequencies (5 Hz or more) tend to increase excitability (an LTP-like effect).

This “rule of frequency” has worked very well for many years, and at a cellular level has been assumed to result from differences in the pattern of Ca^{2+} influx through postsynaptic NMDA receptors that are induced by different stimulation frequencies. However, the recently introduced TMS protocol of theta burst stimulation (TBS), which itself is an extension of common protocols for inducing synaptic plasticity in animal preparations, appears not to follow this rule. TBS in the human motor cortex can very quickly produce an LTP- or LTD-like effect by using bursts at same frequency (three pulses at 50 Hz, repeated five times per second) and intensity without experimentally changing other factors, e.g. the membrane potential (Huang et al., 2007; Huang et al., 2005; Huang et al., 2009). In the case of TBS, the direction of the after effects depends on whether the bursts are delivered continuously (cTBS, producing LTD-like effects) or intermittently (iTBS producing LTP-like effects). When the length of the train of bursts and the pause between the trains are longer than those of iTBS and the train is shorter than that of cTBS there may be no significant after effect (Huang et al., 2005; Huang et al., 2009) (intermediate TBS, imTBS).

The aim of the present paper is to provide a simple model to account for these effects that is based on knowledge of mechanisms of synaptic plasticity at a cellular level. Although TBS may activate pathways containing a variety of transmitter substances, (e.g. GABAergic, synapses: (Hanajima et al., 1998; Stagg et al., 2009; Ziemann et al., 1996), we have limited the model to effects of TBS on glutamatergic synapses, and the NMDA receptor in particular, since their properties are better understood than any other form of synapse. We assume that activation leads to Ca^{2+} entry through the NMDA channel which then triggers cascades leading to LTP or LTD. Importantly, we assume that the processes leading to LTP depend on the rate of Ca^{2+} entry whereas the processes leading to LTD depend on the amount of Ca^{2+} entry (Kemp and Bashir, 2001; Malenka and Nicoll, 1999; Neveu and Zucker, 1996; Sheng and Kim, 2002; Yang et al., 1999), and that both of them are initiated simultaneously by Ca^{2+} entry. The resulting change in synaptic effectiveness (potentiation or depression) depends on the summation of these two effects. This would be consistent with a recent pharmacology study showing that the polarity of the effect of TBS can be reversed by manipulating L-type voltage-gated Ca^{2+} -channels (Wankerl et al., 2010). By fitting appropriate time constants to these processes it is possible to explain the observed consequences of TBS in terms of competition between LTP- and LTD-like effects. Finally we show that it is possible to extend the model to understand how the response to TBS can be modulated by voluntary muscle contraction either before or after TBS is applied. We only focus this model on the effects on healthy subjects. Patients with neurological disorders (e.g. parkinsonism and dystonia) may respond differently to TBS due to their underlying abnormal neural circuits (Edwards et al., 2006; Eggers et al., 2010; Huang et al., 2010).

DETAILS OF THE MODEL

The basic assumption of the model is that TBS produces a mixture of excitatory and inhibitory effects that can summate to yield the observed effects on corticospinal

excitability. Initial work showed that a short burst of 5-15 stimuli at 50 Hz leads to a short latency facilitation followed by a longer-latency and weaker inhibition (Huang et al., 2005; Huang and Rothwell, 2004). Although the mechanism of these short lasting changes is probably quite different to the longer lasting after effects of TBS protocols, the results do illustrate that TMS can have mixed influences on motor cortical excitability which we exploit in the detailed model below. (Please see the supplemental material for the program written in Matlab.)

The model has three stages, each related to a known process that has been shown to occur in one or more types of LTP or LTD. We only focus on the post-synaptic mechanisms of LTP and LTD to keep the current model as simple as possible. Although it is still not clear whether TBS leads to changes in presynaptic plasticity, previous studies using NMDA antagonists indicate post-synaptic interactions are critical for TBS to produce lasting changes in corticospinal excitability (Huang et al., 2007; Teo et al., 2007). In the first stage, we assume that the bursts of 3 stimuli at 50 Hz each result in the build up of a trigger factor, e.g. postsynaptic Ca^{2+} influx, that eventually leads to lasting changes in synaptic efficacy. The concentration of the trigger factor decays exponentially after each burst. When the peak level of Ca^{2+} , for example, after a burst is C , the effect at a time point (t) after the peak level will be

$$C(t) = C \cdot e^{-kt} \quad (1)$$

When bursts are given regularly for n times at t minutes after the peak level, the maximum level of Ca^{2+} after n bursts will be

$$C_{\max}^n = C \cdot (1 + e^{-kt} + e^{-2kt} + \dots + C^{-(n-1)kt}) = C \cdot \frac{1 - e^{-nkt}}{1 - e^{-kt}} \quad (2)$$

Whereas the minimum level after n bursts becomes

$$C_{\max}^n = C_{\max}^n \cdot e^{-kt} = C \cdot \frac{1 - e^{-nkt}}{1 - e^{-kt}} \cdot e^{-kt} \quad (3)$$

In the second stage we propose that the trigger factor leads to production of a “facilitatory” or an “inhibitory” substance designed to be equivalent to activation of different types of protein kinases. It is known that the temporal pattern of Ca^{2+} influx is critical for LTP induction, while the sustained level of Ca^{2+} is important to produce LTD (Yang et al., 1999). Hence, in the model, the “facilitation” accumulates according to the rate of increase in the trigger factor, whereas “inhibition” accumulates more slowly according to the overall level of the trigger factor. Both decay exponentially with time. To simplify the model, only the minimum level of Ca^{2+} is taken as the trigger factor to simulate the second stage. R_f and R_i are proportionality constants of facilitatory and inhibitory “substances” in response to the trigger factors.

$$F_{\min}^n = \sum_{i=1}^n R_f \cdot (C_{\min}^i - C_{\min}^{i-1}) \cdot e^{-(n-i+1)fk} \quad (4)$$

$$I_{\min}^n = \sum_{i=1}^n R_i \cdot C_{\min}^i \cdot e^{-(n-i+1)ik} \quad (5)$$

With iTBS and imTBS, the trigger factor initially rises in the same way but then declines exponentially at the end of each train (i.e. after each 2 s train for iTBS, and after each 5s train of imTBS).

In the last stage of the model, these substances interact with a process that leads to long term changes in synaptic effectiveness. These may be seen as phosphorylation or dephosphorylation of AMPA receptor proteins giving rise to LTP and LTD respectively. The direction and amount of the after effect is determined by the sum of facilitatory and inhibitory “substances” at the end of stage 2. The time course of the after effect is reflected in the changes in corticospinal excitability that we observe experimentally and which build up over minutes after the end of TBS with a sigmoidal profile and decay more slowly, again with a sigmoidal profile. The time course was modelled as follows. If the maximum effect of the conditioning is M and this occurs at time (t_{peak}), then the time from onset to reach half of the maximum effect is $t_{50(o)}$, while the time taken to decline to the half of the maximum is $t_{50(d)}$. Thus the effect at a time point (t) after the TBS will be

$$M(t) = \frac{M \cdot t^{h1}}{t_{50(o)}^{h1} + t^{h1}} \quad (t \leq t_{peak}) \quad (6)$$

$$M(t) = \frac{M \cdot t_{50(d)}^{h2}}{t_{50(d)}^{h2} + t^{h2}} \quad (t > t_{peak}) \quad (7)$$

where $h1$ and $h2$ are power coefficients that describe the steepness of the sigmoid curves.

Parameters for modelling Ca^{2+} changes

First of all, we set C as 1. Because a 3-pulse burst at 50 Hz takes around 40 ms and a burst was given every 200 ms, the t for calculating the decayed effect at the time when the next burst comes is 0.16 seconds. We set the decay constant k to be 1.2. This value is somewhat arbitrary since the model is relatively insensitive to values of k within a very large range.

Parameters for cascades of substances for LTP or LTD

Most parameters in this mathematical model are based on results of previous experiments (Huang et al., 2005; Huang and Rothwell, 2004). Those which could not be obtained from original data were estimated.

The facilitatory “substance” was modelled as accumulating proportional to the rate of the increase of the trigger factor. The proportionality constant was set to 1. The exact value of this is again arbitrary since the overall effect of the model depends on the ratio between this value and that for the inhibitory “substance”. The proportionality constant of the inhibitory “substance” and the time constant of inhibitory and facilitatory substances that both decayed exponentially between bursts are listed in Table 1. These constants for facilitation and inhibition ensured that after 8 single trains of 5s TBS, the amount of each “substance” would be approximately equal.

The decay constant of inhibitory and facilitatory “substances” between trains of iTBS and imTBS (bk) was set to 0.1.

Parameters for modelling the effect after TBS

The maximum effect, M , is the maximum level calculated above for the facilitatory or inhibitory “substances”. To estimate the time of t_{peak} after a TBS, we used a sigmoid curve to fit the known data (Huang et al., 2005), in which the peak inhibitory effect was 5 seconds

after 25 bursts, 7-9 minutes after 100 bursts, and 25 minutes after 200 bursts. These times were chosen according to the time of peak after effects on MEPs after different durations of cTBS. We used the following function to estimate the t_{peak} for an arbitrary number of bursts (*burstnumber*)

$$t_{peak} = \frac{1800 \cdot burstnumber^{3.6}}{130^{3.6} + burstnumber^{3.6}} \quad (8)$$

We set t_{peak} of excitation to be around one fifth of t_{peak} of inhibition, because after 200 bursts, the best MEP facilitation occurred 5 minutes after iTBS while the best suppression occurred at around 25 minutes. The parameters for the onset and decline of the sigmoid curve were chosen by fitting the simulated results with the results of experiments (Table 1).

Metaplastic effects of voluntary contraction

Gentner (2008) recently demonstrated that the inhibitory effect of 20 sec cTBS (cTBS300) originally described by Huang et al. (2005) only occurs if it is preceded by a short period of tonic muscle activity such as is commonly involved when estimating active motor threshold. Without prior muscle activity, cTBS300 produced a slightly facilitatory effect. In contrast, cTBS600 suppressed cortical excitability even without prior contraction. These effects have been termed metaplasticity, which describes how synaptic plasticity can be modulated by prior synaptic activity (Abraham and Bear, 1996). It is generally believed that prior activity may modify presynaptic vesicle release and/or postsynaptic receptor composition or number to cause metaplasticity (Abraham, 2008; Pozo and Goda, 2010). Here we postulate that precontraction changes the rate of calcium influx during TBS so that C, the peak level of Ca^{2+} after a burst, is larger when there is no prior contraction. The metaplastic effects on pathways beneath the postsynaptic membrane that are incorporated into the second stage of the present model have not been studied. Here we assume that the proportionality and decay constants of the inhibitory “substance” were inversely proportional to C^2 , while the decay constant of the facilitatory “substance” was inversely proportional to C. We modelled the condition without prior contraction by increasing C from 1 to 3.

In addition to the precontraction effect, slight voluntary contraction for 1 min immediately after cTBS300 (with prior contraction) reverses the after-effect to facilitation, whereas contraction after iTBS enhances its facilitation (Huang et al., 2008). We have proposed that the build-up of inhibitory after-effect is blocked by contraction while the facilitatory effect is preserved. Thus, to simulate the effect in the model of contraction immediately after cTBS300 and iTBS, we simply removed the inhibitory after-effect leaving behind an unopposed facilitation.

RESULTS

In the first stage TBS causes an increase in the trigger factor, e.g. postsynaptic concentration of Ca^{2+} (Fig. 1, first row). With cTBS, the trigger factor rises rapidly to a peak and then remains at that level until the end of the conditioning (40s). In the second stage, the trigger factor interacts with a process that produces facilitatory and inhibitory “substances”. These could be, for example, different levels of protein kinases in the postsynaptic neurone. The facilitatory “substance” rises at a rate proportional to the rate of increase in the trigger factor, whereas the inhibitory “substance” rises more slowly, proportional to the level of the trigger factor. Thus during cTBS (Fig. 1, second row, right column), the initial rapid rise in the trigger factor causes a rapid increase in the facilitatory “substance” (black line), but this declines gradually thereafter. The sustained increase in the trigger factor during cTBS causes a slower rising but larger increase in the amount of the inhibitory “substance” (dot line). With iTBS (Fig. 1, second row, left column), the rapid increases in the trigger factor at the

start of each 2s train cause a greater production of facilitatory than inhibitory “substances”. With imTBS (Fig. 1, second row, middle column), the amount of each type of “substance” is equal. In the third stage (Fig. 1, third row), the final level of the two “substances” interacts with two corresponding slower processes that may be analogous to phosphorylation/dephosphorylation of membrane bound ion channels responsible for production of LTP/LTD. They rise and fall with sigmoid time courses. Finally (Fig. 1, bottom row), the net effect on MEP amplitudes is modelled as the sum of these positive and negative after effects. Following cTBS, suppression is larger than facilitation and the MEPs are suppressed for many minutes. The opposite occurs after iTBS, whilst after imTBS, suppression and facilitation are matched and there is virtually no net effect on MEP amplitudes.

Fig 2 illustrates the results of cTBS300 with and without prior contraction together with the effect of cTBS600 without prior contraction. cTBS300 with prior contraction produced an inhibitory effect as previously reported (Fig 2A). The absence of prior contraction was modelled by increasing C from 1 to 3 in stage 1 and its corresponding changes in stage 2. This leads to the experimentally observed mild facilitatory effect of cTBS300 without prior activity (Fig 2B). The model also shows that although these changes reverse the effect of cTBS300 to facilitation, the effect of cTBS600 remained inhibitory even in the absence of prior contraction (Fig 2C).

Fig 3 shows the results of cTBS300 and iTBS followed immediately by contraction. By blocking the inhibitory after effect accumulated in stage 2, the effect of cTBS300 with prior contraction was reversed from inhibition to facilitation (Fig 3A), and the facilitatory effect of iTBS was enhanced (Fig 3B).

DISCUSSION

The purpose of our modelling study was to show that it is possible to understand how the opposite effect of two theta burst TMS protocols, which both use the same intensity and basal frequency of stimulation (cTBS and iTBS), can arise from commonly accepted mechanisms of synaptic LTP and LTD. It does not prove that these mechanisms are responsible, only that this is a plausible explanation. The model we used was over-specified, in that it employs more constants than the minimal necessary to account for the data. However, our intention was not to provide the simplest possible mathematical explanation; rather we wished to explore the consequences of standard mechanisms of LTP/LTD. As seen in the figures, there is a difference in the absolute amounts of the real and simulated data. However, this could be readily corrected by rescaling the facilitatory and inhibitory effects. Nevertheless, even without doing this, the model shows that in principle you can account for the polarities and time course of the effects of cTBS and iTBS.

A mixture of excitatory and inhibitory effects produced by the stimulation

The key assumption of the current hypothesis is that TBS produces a mixture of excitatory and inhibitory effects. This would be consistent with the finding that in many systems, both LTP and LTD are triggered by calcium influx to the postsynaptic neuron. Thus, Ca^{2+} influx can promote LTP by phosphorylation of calcium/calmodulin-dependent protein kinase II (CaMKII) as well as LTD via dephosphorylation of cyclic-AMP-dependent protein kinase (PKA) site (Lee et al., 2000). It is still unknown precisely what governs the balance between LTP and LTD. Some authors have proposed that high levels of Ca^{2+} favour LTP whereas moderate levels promote LTD (Kemp and Bashir, 2001; Malenka and Nicoll, 1999; Sheng and Kim, 2002). In fact, the temporal pattern of calcium increase may be even more important than the absolute level. Neveu and Zucker (1996) found no distinct calcium threshold for inducing LTP and LTD, whilst Yang et al (1999) demonstrated that LTP is triggered by a sudden increase in the postsynaptic calcium level, whereas a more prolonged

modest rise of the calcium level reliably triggers LTD. This may be because a sudden influx of Ca^{2+} desensitises inositol triphosphate receptors (InsP_3Rs), which can release Ca^{2+} from internal stores and are crucial for the production of LTD (Bezprozvanny et al., 1991). This argument is further supported by a study showing that partial blockade of NMDA receptors to slow Ca^{2+} influx results in a conversion of LTP to LTD while dysfunction of InsP_3Rs results in a conversion of LTD to LTP (Nishiyama et al., 2000).

The assumption in our model is equivalent to saying that calcium influx will simultaneously promote both LTP and LTD and that the final outcome will be determined by which is more powerful. Given the common role of calcium in both processes, this seems a reasonable proposal, and is supported by a recent finding showing that LTP and LTD can occur simultaneously at a central synapse in the leech (Burrell and Li, 2008). In reality the situation may be even more complex. Epidural recording of descending volleys of MEPs showed that cTBS suppressed mainly the I1 wave, while iTBS enhanced only the later I waves (Di Lazzaro et al., 2008; Di Lazzaro et al., 2005; Di Lazzaro et al., 2010). This may mean that the LTP and LTD-like consequences of TBS are manifested to different extent at different cortical synapses. LTD-like consequences might be more powerful within the circuits generating the I1 wave whereas LTP-like effects might be stronger in later I-wave pathways.

According to this interpretation, if TBS is given in short trains, as in the iTBS paradigm, then a large amount of Ca^{2+} may quickly enter the postsynaptic membrane, desensitizing InsP_3Rs and promoting phosphorylation of CaMKII sites. After a short train, this may not reach the threshold for LTP and may instead cause a short-term potentiation (STP) effect (Malenka and Nicoll, 1999). The level of calcium is likely to decline quickly towards baseline during the pause between trains so that when the next short train is given a new wave of Ca^{2+} influx produces more phosphorylation. After a few trains, the effects summate to reach the threshold to cause LTP after the end of the stimulation. This would be consistent with data from animal studies suggesting that both excitatory and inhibitory effects can summate to produce more powerful and longer lasting effects when pulses are given at a sufficiently high frequency. (Beierlein et al., 2003; Schmidt and Perkel, 1998). In contrast, when the bursts are given continuously, as in the cTBS paradigm, the rate of Ca^{2+} influx may decrease gradually over the course of stimulation. This could allow a recovery in function of the InsP_3Rs and promote a longer lasting, moderate, rise in the calcium, which would favour dephosphorylation of PKA sites and induction of LTD. When the length of a train is intermediate (as in the imTBS paradigm), the effects of the initial sharp rise in $[\text{Ca}^{2+}]$ are matched by a degree of recovery in InsP_3R function, producing a state of equilibrium between phosphorylation /dephosphorylation, and therefore LTP/LTD.

The role of Ca^{2+} in determining the direction of the after-effect of TBS is further supported by a recent study showing that drugs modifying Ca^{2+} channels may change the polarity of LTP/LTD-like effects produced by TBS (Wankerl et al., 2010). When 30 mg of nifedipine, a Ca^{2+} -channel blocker, was given beforehand, cTBS300 without prior contraction induced inhibition rather than potentiation. Moreover, a smaller dose of 15 mg of nifedipine together with very short 1.5-min contraction (neither of which had any effect when given alone) could summate to produce an effect similar to that of 30 mg of nifedipine.. The above findings are compatible with the current model that a Ca^{2+} -blocker and prior contraction both slow down and reduce the amount of Ca^{2+} influx to the post-synaptic membrane and result in the inhibition that follows cTBS300.

This theory may also help to explain the effects of some other rTMS paradigms. For example 10 minutes or more 1Hz rTMS conditioning usually leads to LTD-like effects (Chen et al., 1997; Touge et al., 2001) whereas rTMS at 5 Hz leads to LTP-like changes. This

contrasts with animal data where long trains (20 minutes) of stimulation at both 1 and 5 Hz can produce reliable LTD effects. However, in the animal experiments, 5 Hz trains are delivered as a long continuous burst whereas in humans, 5 Hz stimulation is usually delivered in single short trains (Berardelli et al., 1998; Maeda et al., 2000; Wu et al., 2000) or more commonly in repeated short trains (Gilio et al., 2002; Siebner et al., 1999). It is therefore possible that the opposite effect of the 1 Hz and 5 Hz rTMS paradigms on cortical excitability in human studies is due to the pattern of stimulation (continuous vs. intermittent) rather than the frequency. This argument is further supported by a recent study showing that pauses are required for 5 Hz rTMS to produce excitatory after effects whilst continuous 5 Hz stimulation leads to inhibition (Rothkegel et al., 2010). This basic concept can also explain why the after-effects of the recently introduced quadripulse stimulation method (QPS) also depend on the intervals between pulses within a burst (Hamada et al., 2008). It is possible that pulses at shorter inter-pulse intervals (e.g. 1.5-10 ms) cause short and quick calcium influx and produce facilitatory effects, while those at longer intervals (e.g. 30-100 ms) favour inhibitory effects. If the facilitation produced by a pulse is stronger and lasts for a shorter time than inhibition then it could explain why facilitation occurs when the interval between pulses is short while longer inter-pulse intervals gradually accumulate an inhibitory effect.

Although we favour the idea of concurrent processes of LTP and LTD, an alternative explanation of the opposite effects of cTBS and iTBS is possible by invoking the concept of “metaplasticity”. Thus the early part of a cTBS paradigm could produce a period of LTP which then could lead to a metaplastic response to the later part of the train and eventual suppression of excitability. Indeed, such a process has been invoked by some authors to explain several results in the animal literature. When Larson et al. (Larson et al., 1986) first developed the theta burst pattern of stimulation, they found that the LTP effect was considerably smaller when 20 bursts were used compared with 10 bursts. 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 some studies demonstrated that excessive stimulation of TBS in a short period of time resulted in reduced LTP in several areas of brain slices (Abraham and Huggett, 1997; Christie et al., 1995). In all cases, reduced LTP with longer trains could have been the result of a metaplastic response to the earlier portion of the train.

However, such mechanisms cannot explain why overstimulation, or in the human data, cTBS, has to be completed within such a short time window. Even though depotentiation only occurs within a certain time window after induction of LTP, the duration is usually longer than in the examples above (Burette et al., 1997; Huang et al., 1999; Larson et al., 1993). In addition the concept could lead to the implausible situation that a long train of continuous stimulation produces an initial facilitation followed by a later metaplastic response leading to inhibition which, if stimulation continues, will itself lead to a further metaplastic reversal to facilitation etc.

Finally it should be noted that more conventional metaplastic effects such as those produced by muscle contraction before or after TBS (Gentner et al., 2008) could readily be incorporated into the model by assuming that they lead to changes in Ca^{2+} entry and the time constants of processes leading to potentiation and depression. Interestingly, these metaplastic adjustments of the model parameters also predicted that the inhibitory response to cTBS600 was unchanged in the absence of prior contraction. This suggests that the self-priming mechanism proposed by Gentner and colleagues may not be required to explain the constant inhibitory effect of cTBS600. The current model also supports the idea that tonic muscle contraction immediately after TBS prevents expression of inhibition in the model's

third stage resulting in facilitation (rather than depression) after cTBS300 and enhanced facilitation after iTBS (Huang et al., 2008).

The major purpose of this model is to explain how TBS produces opposing effects by adjusting the pattern of stimulation and to formalize our previous hypothesis about the dual nature of TBS effects. With the theta burst paradigm, continuous stimulation tends to produce LTD-like results, while a short train or intermittent short trains of stimulation tend to have an LTP-like effect. Such considerations could mean that potentiation protocols may require short pause to achieve maximum effect. If an excitatory paradigm (e.g. iTBS) is prolonged, then potentiation may gradually decline because of a slow build up of inhibition. Indeed, compatible with our prediction, a recent study demonstrated that prolonged iTBS with 1200 pulses produced inhibition rather than potentiation (Gamboa et al., 2010). In contrast, the same study showed that prolonged cTBS produced potentiation instead of inhibition. This may illustrate a potential limitation in our model, since the model suggests that it may be necessary to extend an inhibitory protocol (e.g. cTBS) to optimise depressive effects. A further study and model involving more complicated plasticity mechanisms, e.g. metaplasticity and heterosynaptic plasticity, may be required to address this point.

CONCLUSION

We hypothesise that repetitive burst (or pulse) stimulation can induce a mixture of facilitatory and inhibitory effects, and that the balance between them can be modified by changing the pattern of stimulation. We also successfully predicted from this model that longer periods of stimulation may not always produce larger effects, particularly for iTBS. In the future, it may be possible to develop new protocols of TBS by manipulating parameters in the model, e.g. intervals, pulse numbers and train numbers, before they are tested experimentally.

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Figure 1. Results of a simple model that accounts for the different long lasting effects of cTBS, imTBS and iTBS

The model has three stages, represented by the three rows of graphs. The after effects in stage 3 are superimposed with the experimental results from our previous work. In stage 3, the left Y axis is the arbitrary units for the simulated results, while the right Y axis is the % of change of the MEP size for the experimental results.

Figure 2. Simulated results of cTBS with and without prior muscle contraction

cTBS300 with prior muscle activity shows a suppressive effect (A), while the effect of cTBS300 without prior contraction becomes slightly facilitatory (B). cTBS600 still has an inhibitory effect even there is no muscle contraction beforehand. The after effects in stage 3 are superimposed with the experimental results from our previous work and those from the study of Gentner et al. (Gentner et al., 2008) with permission. The left Y axis is the arbitrary units for the simulated results, while the right Y axis is the % of change of the MEP size for the experimental results.

Figure 3. Simulated results of cTBS300 and iTBS followed by 1-min contraction

The effect of cTBS300 (with precontraction due to measurement of active motor threshold) was reversed from inhibition to facilitation (A), while the facilitatory effect of iTBS was enhanced by the 1-min contraction (B). The after effects in stage 3 are superimposed with the experimental results from our previous work. The left Y axis is the arbitrary units for the simulated results, while the right Y axis is the % of change of the MEP size for the experimental results.

Table 1

Summary of the parameters used in the model. The parameters and their biological relevance, suggested values and the source of those values are summarized. In addition, how sensitive of each parameters to the results is identified

Parameter	Value	Biological relevance	Source of that value	Sensitivity to results
Parameters for stage 1				
C	1	Peak Ca^{2+} level after a burst	Arbitrary	No
t	0.16	Interval between bursts	A burst takes around 40 ms and a burst was given every 200 ms	Yes
k	1.2	Decay constant of Ca^{2+} level	Arbitrary	No
Parameters for Stage 2				
Rf	1	Proportionality constant of facilitation	These constants for facilitation and inhibition ensured that after 8 single train of 5s TBS, the amount of each "substance" would be approximately equal in the condition without prior contraction.	Yes.
Rk	0.01/C	Decay constant of facilitation		
Ri	0.14/C ²	Proportionality constant of inhibition		
ik	0.055/C ²	Decay constant of inhibition		
bk	0.1	Decay constant for the declines between trains in iTBS and mTBS	Arbitrary	No
Parameters for Stage 3				
$t_{peak(i)}$	Calculated	Time point where maximum inhibitory after-effect occurs	Calculated from the pulse number Based on previous experimental results.	Yes
$t_{peak(l)}$	$t_{peak(i)}/5$	Time point where maximum facilitatory after-effect occurs	The best MEP facilitation occurred at 5 min after iTBS while the best suppression occurred at 25 min after cTBS	Yes
	Inhibition	Excitation		
$h1$	2.5	3	The parameters were chosen by fitting the simulated results with the results of experiments.	Yes
$h2$	4	2		
$T_{50(o)}$	$t_{peak(i)}/5$	$t_{peak(l)}/4$		
$T_{50(d)}$	$t_{peak(i)} * 1.1$	$t_{peak(l)} * 2$		
Parameter changed without prior voluntary contraction				
C	3	Without prior contraction, the rate of calcium influx is increased.	Arbitrary	Yes