Review: Repetitive Transcranial Magnetic Stimulation over the Human Primary Motor Cortex for Modulating Motor Control and Motor Learning

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that is capable of producing after-effects outlasting the stimulation for minutes to more than an hour. Varied paradigms and targets of the stimulation may produce different brain modulations corresponding to the changes of specific cortical plasticity. Conventional low-frequency rTMS depresses the cortical excitability, while high-frequency rTMS enhances the cortical excitability. More recently developed patterned rTMS paradigms do not follow the rule of frequency and produce inhibition and facilitation by adjusting the stimulus patterns. The ability of brain modulation makes rTMS an ideal tool to study the brain function in conscious humans. Here we focused our review on the effect of applying rTMS over the primary motor cortex (M1) on motor control and motor learning. We confirmed that rTMS modulated motor control and learning in line with its ability of changing cortical excitability. However, inconsistency and variability were among studies. Such inconsistency could be due to (1) different protocols and motor tasks in different studies, (2) poor efficiency of rTMS and (3) complicated neural network and indirect or remote effects induced by rTMS. The recent evolution of patterned rTMS, such as theta burst stimulation (TBS), might provide opportunities for in-depth understanding the effect of rTMS on motor performance and take a step closer to the potential use of rTMS in disease therapy.

Keywords: Repetitive transcranial magnetic stimulation (rTMS), Theta burst stimulation (TBS), Cortical plasticity, Motor evoked potential (MEP)

1. Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive approach to stimulate cortical neurons with negligible discomfort. A very short duration high intensity electrical current in the magnetic coil produces a transient magnetic field penetrating the intact scalp and skull. As soon as the magnetic field is developed and subsequently decays in less than 1 ms duration, an electrical field forms just beneath the stimulating coil. Following the changes in electrical field, electric current elicits volleys from the neuronal axons that synapse on pyramidal neurons. Propagation of the axonal current induces postsynaptic potentials and the final physiological responses [1,2]. Such indirect neuronal responses, termed as I waves, contribute to the major component of the TMS evoked potential. The D wave, which is directly activated from the neuron, is usually small or absent in weak TMS, and can be only detected by TMS of certain coil orientations [3]. Characteristics and settings of the stimulating coil, in parallel with varied magnetic waveforms (monophasic, biphasic, sinusoidal, etc.), guaranteed the alteration of the input/output response of the stimulated brain [4-9]. The net physiological effect of TMS pulses relies on the projections of synapses that are excited by the electrical current coupled with imposed magnetic field.

In contrast to single pulses of TMS that elicit short responses in the brain, repetitive TMS (rTMS) trains can produce relatively long-lasting changes outlasting the stimulation for minutes to more than an hour in cortical excitability and regional brain activities. These long-lasting changes are closed to long-term potentiation (LTP) and long-term depression (LTD) that form the basis of neuroplasticity [10,11]. Beyond the factors relative to the coil design, the after-effects of rTMS depend much on the

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parameters of stimulus pulse number, intensity and frequency of the magnetic stimulation. Conventionally, rTMS can be categorized by the frequency of stimulating train. A single continuous train of low frequency rTMS (< 5 Hz, typically at around 1 Hz) was found to suppress the cortical synaptic excitability in the human motor cortex [12-14]. On the contrary, a higher frequency train(s) of rTMS (≧ 5 Hz) tends to potentiate the cortical excitability [13,15]. Nevertheless, recent studies have demonstrated that the cortical excitability can be modified by some other patterned magnetic trains, such as paired-pulse rTMS [16-19], theta burst stimulation (TBS) [20,21], and quadripulse stimulation (QPS) [22]. These paradigms were designed to reinforce the after-effects of rTMS by improving the efficiency of the stimulation protocol and enhancing the retention of changes in cortical excitability. The evolution of rTMS paradigms is helpful to elucidate the regional activity and behavioral relevance of specific cortical neurons.

2. rTMS over M1 contralateral to the movement

The majority of the descending pyramidal fibers decussate at medulla, so movements of the limbs are primarily controlled by the contralateral hemispheres. The effect of rTMS on the motor cortical excitability is commonly evaluated by the TMS-induced motor evoked potential (MEP) recorded from muscles contralateral to the stimulated M1. Therefore, the behavioral effects of rTMS given to M1 were firstly and more commonly evaluated in the limbs contralateral to the stimulated M1.

The stimulus intensity of rTMS is commonly adjusted by the motor threshold, including rest motor threshold (RMT) and active motor threshold (AMT). The RMT and AMT are the least intensity of transcranial magnetic stimuli to successfully elicit motor responses when the subject is at rest and is slightly activating the target muscle, respectively. AMT is known to be lower than RMT when measured in the same subject. In this review, when supra- or sub-threshold is mentioned, the threshold indicates RMT unless classified elsewhere.

2.1 Low-frequency rTMS

Lower frequency has been applied over a supra-threshold (115% RMT) rTMS train at 0.9 Hz to contralateral M1 for 15 minutes and found no interference with maximal finger tapping speed in both hands [12]. Similar low-frequency rTMS also failed in altering the finger tapping speed [23], thumb opposition speed [24], peak force, peak acceleration of the target muscles [14,25], hand tapping speed and velocity of grasp following reaching [26]. Contradictory results were found by Wassermann et al [27], who reported that the maximal index-tapping rate was hastened by 1-Hz rTMS (180 pulses) at 125% RMT given to contralateral M1. Because the high stimulus intensity, we cannot rule out the possibility that the current overflowed to the areas adjacent to M1, e.g. premotor and frontal cortices, to cause the behavioral effect in the last study.

Although the results were not consistent, motor control was paradoxically affected by low-frequency rTMS of sub-threshold intensity over the contralateral M1 in several studies [28-32]. Jänke and colleagues proposed that maximal index tapping speed of the dominant hand was slowed down and lost the superiority to the non-dominant hand after delivering 1-Hz rTMS at 90% RMT to the dominant hemisphere for 10 minutes [28]. In addition, the 10-min rTMS over left M1 decreased the self-paced tapping speed in both hands, while the speed of other externally-paced finger tapping tasks and fastest sequential index tapping were not affected [29]. Beyond the measurement of finger tapping rate, the synchronization between the finger movement and externally pacing signal was studied [30]. Research has shown that the movement synchrony of the metronome-paced finger tapping was improved when the 1-Hz rTMS of 90% RMT was applied to the contralateral M1 for 15 minutes. However, the maximal impact force of the tap and the ability of correcting phase perturbation were not altered. Repeating the same 15-minute rTMS session twice with an one-minute interval, however, resulted in no alternation in the contralateral motor performance and rate of fastest index tapping [31]. As for reaction time tasks, research reported that sub-threshold 1-Hz rTMS (80% AMT; 20 minutes) over contralateral either M1 or premotor cortex lengthened the reaction time of visually-cued choices [32]. Regarding the force and velocity of movement, they have been reported to stay constant [12,14,24-26,29-31] or get worse [28,32] after low-frequency rTMS.

In a metronome-paced (0.5 Hz) ballistic finger pinch task, 1-Hz rTMS over the contralateral M1 canceled the post-practice improvement in the pinch force and pinch acceleration [25,33]. It was noteworthy that the supra-threshold rTMS train (115% RMT, 15 minutes) did not directly regulate the peak force and the peak acceleration, but removed the post-practice progression. Interestingly, the improvement in force and acceleration was retained if the rTMS was postponed 6 hours after the practice [25]. In a force-field learning experiment, 1-Hz rTMS (120% RMT, 15 minutes), which was administered to the contralateral M1 after the learning epoch, did not reduce the gains from learning [33]. While applying rTMS before force-field learning, sub-threshold 1-Hz rTMS (90% RMT, 15 minutes) over contralateral M1 showed no effect during the learning epoch, but worsen the performance in the re-test epoch at 24 hours after the learning [34]. A similar protocol (1-Hz rTMS, 90% RMT, 10 minutes) given before the training of index tracking movement exerted no influence on the training effect during the training sessions and the retention tests at 2 and 10 minutes post-training [35].

Above studies illustrated that sub-threshold low-frequency rTMS before motor learning produced no immediate effect on the performance [34,35]. However, the delayed onset learning deficiency caused by rTMS suggested that contralateral M1 was involved in the "off-line learning" or "motor memory consolidation" occurring after the training sessions [34]. The involvement of M1 in the consolidation of motor memory was further investigated [36,37]. The studies indicated that 1-Hz rTMS (90% RMT, 10 minutes) administered right after motor training did not alter the immediate outcome of sequential learning. However, the gains from learning (sequential movement speed) measured 12 hours later were significantly worsened by the stimulation [36]. Besides, the decline in off-line learning consequence was not observed if sleep was inserted within 12 hours after training. Similar to previous reports, rTMS administered 2 hours after training did not affect the progression in sequential movement. Hotermans and colleagues also showed that the intervention of rTMS on off-line learning only occurred at 30 minutes, but not at 4 hours, 24 hours, and 48 hours, after the training blocks [37]. One possible mechanism of the cancelation of motor learning caused by 1-Hz rTMS is the reversal of plasticity, i.e. depotentiation and de-depression that has been shown in the animal preparations [38] and recently reported in human [39]. The reversal of plasticity requires the second stimulation, as the 1-Hz rTMS in above studies, to be given within a certain time window after plasticity is induced. This is compatible with the time-dependent property of the 1-Hz rTMS-induced learning cancelation effect.

2.2 High-frequency rTMS

Short trains of high-frequency rTMS have been commonly used to create "virtual lesion" in the studied area. The "virtual lesion" is induced by the interference of the pulse(s) of rTMS and the mechanism is known to be different from synaptic plasticity induced by longer trains of rTMS. A short train of 15-Hz rTMS (110% RMT, 2.3 seconds) to contralateral M1 during finger tapping sequences produced significant MEPs and corresponding jerky movements that clearly interrupted the tapping sequence [40]. Another study used similar 15-Hz stimuli at the intensities around AMT (80-120% AMT, 2 seconds) to investigate the intensity modulating effect [41]. At the identical stimulus intensity, the accuracy and timing of sequential finger movement were influenced more in the complex sequence than in the simple one. The intensity of stimulation required to be augmented to disrupt the simple sequence. Similar perturbation from sub-threshold 5-Hz stimulation (90% RMT) was also noted in the grooved pegboard test [42]. When performing the grooved pegboard test, concurrent rTMS lengthened the total execution time. Above results suggest that the contralateral M1 is not only a motor executive area, but is also capable of organizing complex movement sequences. The motor performance interfered by the "virtual lesion" induced by high-frequency rTMS in M1 supports the idea that M1 is involved in the motor control.

In contrast to the real-time effect caused by a short train, a longer train of high-frequency rTMS modulates the cortical excitability outlasting the stimulation for a period of time [27,43-46]. High-frequency rTMS is intuitively supposed to enhance the motor performance because of the facilitatory response in corticospinal excitability. Many, but not all, experimental results support this argument. Wassermann et al. reported a non-specific enhancement of contralateral maximal index-tapping rate after applying 20-Hz rTMS (100% RMT, 400 pulses) to the M1, prefrontal, or parietal areas [27]. A sub-threshold 5-Hz rTMS train (90% RMT) was found no contribution to a simple ballistic movement and a choice reaction task, even if the cortical activity in electroencephalogram (EEG) during the period of movement anticipation and the cortical excitability (MEP) were significantly augmented by the rTMS [43,44]. The amplitude, duration, peak velocity, and peak acceleration of ballistic index abduction were not altered by the 1800 magnetic stimuli, either [43]. On the contrary, Strens et al. [45] reported that 150 pulses of sub-threshold 5-Hz rTMS (90% AMT) over contralateral M1 significantly increased finger tapping force. Moreover, sub-threshold 10-Hz rTMS (90% RMT, 1000 pulses) significantly shortened the movement time of complex sequential movements as compared with sham stimulation [46]. The simultaneous functional images during behavioral tests suggested that the improvement in movement time was likely due to the reinforcement of cortico-subcortical network related to motor learning.

Researchers paid less attention to the effect of high-frequency rTMS on motor learning. While executing a procedural learning task, sub-threshold 5-Hz stimulation (90% RMT) on the contralateral M1generated no behavioral effect [42]. Other research indicated that the total success number of sequential movements was segmented using 10-Hz rTMS (80% RMT, 2 second) before each training block in comparison with the sham stimulation [47]. Besides, the average execution time of each finger movement was significantly shorter in the rTMS group at the end of the training. In contrast to low-frequency rTMS that worsen or has no effect on motor learning tasks [34,35], high-frequency rTMS over contralateral M1 tends to promote motor learning throughout the training process when it was given beforehand.

In a two-dimensional position aiming task, 5-Hz rTMS (90% AMT, 10 seconds) could not modify the motor performance during the period of motor memory consolidation [48]. The result is in contrast to the force-field studies using low-frequency rTMS [33,34]. This may imply that the motor learning is easier to be disrupted but harder to be improved. However, it could be simply because a 10-sec train of 5-Hz rTMS was too short to produce any significant effect.

2.3 Paired-pulse rTMS

Paired-pulse rTMS utilized two equal or uneven serial stimuli as one unit-pulse (Figure 1) [16-19]. Equal pairs of rTMS were found to be inhibitory at inter-stimulus interval (ISI) of 3-ms (80% AMT; 500 pairs at 0.6 Hz) [17] and facilitatory at ISI of 1.5 ms (supra-threshold; 360 pairs at 0.2 Hz) [18,19]. In contrast, Sommer et al. proposed an uneven paired-pulse paradigm to induce bidirectional plasticity [16]. The leading and following pulses of each pulse pair were termed as "conditioning stimulus" with 90% AMT and "test stimulus" with 120% RMT, respectively. By adjusting ISI between the conditioning and test pulses, uneven paired-pulse rTMS produces bidirectional modulation of the cortical excitability. A shorter ISI (e.g. 2 or 3 ms) favors inhibition, while a longer ISI (e.g. 10 ms) tends to produce a facilitatory effect.

Research has shown that even paired-pulse rTMS over M1 (around AMT, 180 pairs) reduced the rate of force decline in a 10-second maximal voluntary pinch grip in the contralateral hand [49]. Nevertheless, neither the facilitatory (ISI = 10 ms) nor inhibitory (ISI = 3 ms) uneven paired-pulse rTMS (900 pairs at 1 Hz) to M1 altered the maximal finger tapping speed of the contralateral hand in healthy subjects [23].

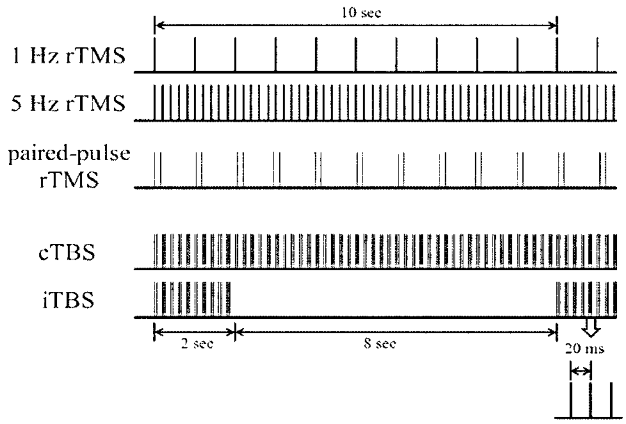

Figure 1. Illustration for conventional rTMS trains of low (1 Hz), high (5 Hz) frequency and patterned rTMS including paired-pulse cTBS, and iTBS.

2.4 Theta burst stimulation

Theta burst form of rTMS was firstly proposed by Huang et al [20]. Each burst is composed of three 50-Hz pulses and the bursts are delivered in 5 Hz (theta band). By adjusting the pattern of burst stimulation, TBS exhibits distinct effects on cortical excitability: continuous TBS (cTBS) that gives bursts in an uninterrupted train for 20 or 40 seconds produces inhibition for 20 or 60 minutes, respectively; while intermittent TBS (iTBS) that gives burst in short (2 second) trains intermittently for around 3 minutes produces facilitation for 20 minutes or so (Figure 1). The advantages of TBS compared to conventional rTMS lie in the significantly lesser exposure to the magnetic stimuli and longer retention of modulating effects.

After delivering 20-second cTBS (cTBS300; 80% AMT, 300 pulses) over M1, simple choice reaction time of finger tapping in bilateral hands was altered in different ways [20]. The contralateral reaction time was significantly prolonged at 10 minutes after cTBS300. As for the hand ipsilateral to the stimulated M1, the reaction time significantly shortened at 30 minutes after the stimulation. In spite of the changes in reaction time, accuracy of force control was not altered by the TBS. However, the alteration in reaction time was not seen in different tasks after 40-second cTBS (cTBS600; 80% AMT, 600 pulses) given to the contralateral M1 or S1 [50]. The temporal relationship between changes in grip and load forces of an anticipatory grip-force scaling task was found to be altered by cTBS600. The deficit in force precision post-TBS was also noted in [51].

In concern with the facilitatory iTBS (80% AMT, 600 pulses), stimulation over contralateral M1 did not affect the peak velocity, peak acceleration, and peak amplitude of serial index abduction blocks [52]. In addition, iTBS showed no effect on the practice-related changes in kinematic parameters of fast index abduction task. Compared with sub-threshold high-frequency rTMS, studies have shown that iTBS produces similar or even stronger facilitatory effect on the cortical excitability [20,43,44]. Thus, iTBS may preferentially elicit changes in more complex sequential movements as seen in high-frequency rTMS [46]. Further studies are required to address this issue.

In contrast to the behavioral effect induced by TBS, several studies demonstrated that motor activities in the limb could modulate the after-effects of TBS given to contralateral M1. Neither cTBS nor iTBS produced after-effect on the size of MEPs when a slightly tonic voluntary contraction was given during TBS. A 1-min similar contraction performed immediate after TBS reversed the inhibitory effect of cTBS300 and enhanced the facilitaory effect of iTBS [53]. Interestingly, the similar 1-min contraction did not modify the effect of cTBS600 [54]. Voluntary motor activities before TBS could also modulate the polarity of after-effect of TBS which is probably through the mechanism of metaplasticity [55,56].

3. rTMS over M1 ipsilateral to movement

A normal functioning brain requires the balance between two hemispheres [57,58]. The ipsilateral hemisphere interacts and works with the contralateral hemisphere to control the motor movement. Stimulation over M1 can evoke MEPs and silent periods in the ispilateral muscles [59]. Meanwhile, voluntary muscle contraction changes the excitability of the ipsilateral cortex [60]. Moreover reciprocal hyperactivity in the contraleteral hemisphere has been observed in patients with unilateral stroke [61,62]. Such influence of ispilareal cortex may involve, in part, the GABAergic transcallosal inter-hemispheric inhibition [63-65]. Hence the effect of rTMS on ipsilateral movement has also been studied.

3.1 Low-frequency rTMS

Supra-threshold 0.9-Hz rTMS (115% RMT, 15 minutes) did not alter the maximal finger tapping speed in ipsilateral hand [12]. The performance in Purdue Pegboard test was not changed by an ipsilateral 0.5-Hz protocol (80% RMT, 10 minutes) [66]. In contrast, several studies rather reported augmented ipsilateral motor performance after low-frequency rTMS [29,67]. Dafotakis et al. showed both 1-Hz rTMS (100% RMT, 10 minutes) on the left and right M1s hastened ipsilateral finger and hand tapping speed and the speed of grasp aperture, while the hastening was more pronounced in the left hand [26]. Stimulation of 600 pulses at 90% RMT of 1 Hz speeded up the ipsilateral sequential finger tapping [29]. A longer sub-threshold 1-Hz rTMS train (90% RMT, 25 minutes) was applied to the ipsilateral M1 to test the influence of ipsilateral low-frequency rTMS to varied movement tasks [67]. Their findings indicated that the rTMS decreased the inter-tapping interval (ITI) of finger movement execution ipsilaterally only in the externally paced sequential movements, but not in the self-paced or maximal speed sequential movements. In another aspect, the ITI improvements were significantly related to movement complexity. Also, the externally paced movement of higher complexity received more apparent speeding effect from the 1-Hz rTMS train. Ipsilateral low-frequency rTMS also interacted with active movement [67]. 1-Hz rTMS (90% RMT, 20 minutes) improved ITI of sequential finger movement immediately and at 15 and 30 minutes after stimulation. However, if the motor test was performed at

Table 1. Low-frequency rTMS over contralateral M1 and motor control.

Authors and year	Stimulus frequency	Stimulus amplitude	Total number of pulses	Significance in motor parameters (N. S. means no significance)
Supra-threshold stimulation, figure-of-eight coil				
Chen et al., 1997 [12]	0.9 Hz	115% RMT	810	N. S.
Muelbacher et al., 2000 [14]	1 Hz	115% RMT	900	N. S.
Sommer et al., 2002 [23]	1 Hz	120% RMT	900	N. S.
Rossi et al., 2000 [24]	1 Hz	110% RMT	900	N. S.
Muellbacher et al., 2002 [25]	1 Hz	115% RMT	900	N. S.
Dafotakis et al., 2008 [26]	1 Hz	100% RMT	600	N. S.
Wassermann et al., 1998 [27]	1 Hz	125% RMT	180	Hasten movement speed (finger tapping)
Sub-threshold stimulation, figure-of-eight coil				
Jänke et al., 2004 [28]	1 Hz	90% RMT	600	Decelerate movement (maximal and self-paced finger tapping)
Kobayashi et al., 2004 [29]	1 Hz	90% RMT	600	N. S.
Doumas et al., 2005 [30]	1 Hz	90% RMT	900	Better movement synchrony with external cue (auditory)
Lee et al., 2003 [31]	1 Hz	90% RMT	1800	N. S.
Schlaghecken et al., 2003 [32]	1 Hz	80% AMT	1200	Lengthen choice reaction time

Table 2. High-frequency rTMS over contralateral M1 and motor control.

Authors and year	Stimulus frequency	Stimulus amplitude	Total number of pulses	Significance in motor parameters (N. S. means no significance)
During movement, figure-of-eight coil			Time for interfering	
Chen et al., 1997 [40]	15 Hz	110% RMT	2.3 seconds	Jerky movements with MEPs
Gerloff et al., 1998 [41]	15 Hz	80-120% AMT	2 seconds	Enhance accuracy or timing errors in sequential movement, especially in complex sequence
Pascual-Leone et al., 1998 [42]	5 Hz	90% RMT	not available	Disturb sequential movement task (grooved pegboard test)
Supra-threshold stimulation, figure-of-eight coil				
Wassermann et al., 1998 [27]	20 Hz	100% RMT	400	Hasten movement speed (finger tapping)
Sub-threshold stimulation, figure-of-eight coil				
Agostino et al., 2007[43]	5 Hz	90% RMT	1800	N. S.
Holler et al., 2006 [44]	5 Hz	90% RMT	1500	N. S.
Yoo et al., 2008 [46]	10 Hz	90% RMT	1000	Hasten movement speed (complex sequential finger pressing)

Table 3. Patterned rTMS over contralateral M1 and motor control.

Authors and year	Stimulus frequency	Stimulus amplitude	Total number of pulses	Significance in motor parameters (N. S. means no significance)
Paired-pulse				
Sommer et al., 2002 [23]	1 Hz	90, 120% RMT	900 pairs	N. S.
Benwell et al., 2004 [49]	0.2 Hz	100% AMT	180 pairs	Reduce rate of force loss during maximal voluntary contraction
cTBS				
Huang et al., 2005 [20]	5 Hz	80% AMT	300	Lengthen reaction time at 10 minutes after TBS
Schabrun et al., 2008 [50]	5 Hz	80% AMT	600	Changes in temporal relationship between grip and lift force
Stefan et al., 2008 [51]	5 Hz	70% RMT	300, 600	Degrad precision of force (grip force)
iTBS				
Agostino et al., 2008 [52]	5 Hz	80% AMT	600	N. S.

30 minutes after rTMS, the ITI improvement never showed up. Although many studies showed improvements in ipsilateral performance, Jänke et al. found that the sub-threshold 1-Hz rTMS (90% RMT, 10 minutes) decelerated the ipsilateral self-paced finger movement with convenient speed [28].

In normal participants, the ipsilateral low-frequency rTMS is somewhat associated with the improvement in movement speed in many [26,29,67], but not all studies [12,28,66]. This benefit could be due to a reciprocal activation associated with the deprivation of interhemispheric inhibition from the contralateral hemisphere. Some studies of the ipsilateral M1 rTMS revealed functional variance between left and right M1s [26,40]. These discrepancies suggested the functional topography asymmetry during human development.

3.2 High-frequency rTMS

The effect of high-frequency rTMS over the ipsilateral motor performance has been less studied. Similar to the effect of contralateral stimulation, employing a short train of supra-threshold high-frequency rTMS over ipsilateral M1 during finger movement sequences enhanced the timing errors [40]. The rTMS induced more timing errors in complex sequence than in simple one. With complex sequence the ipsilateral stimulation induced more timing errors in the left hand than in the right hand. Furthermore, the timing errors still presented in the left hand even when the rTMS train has ceased. These findings demonstrated that altering the left M1

Table 4. Low-frequency rTMS over ipsialateral M1 and motor control.

Authors and year	Stimulus frequency	Stimulus amplitude	Total number of pulses	Significance in motor parameters (N. S. means no significance)
Supra-threshold stimulation, figure-of-eight coil				
Chen et al., 1997 [12]	0.9 Hz	115% RMT	810	N. S.
Dafotakis et al., 2008 [26]	1 Hz	100% RMT	600	Hasten movement speed (finger tapping, hand tapping, and movement to reach for the left side, hand tapping for the right side)
Sub-threshold stimulation, figure-of-eight coil				
Jänke et al., [28]	1 Hz	90% RMT	600	Decelerate movement (self-paced finger tapping)
Kobayashi et al., [29]	1 Hz	90% RMT	600	Hasten movement speed (ipsilateral sequential finger tapping)
Weiler et al., 2008 [66]	0.5 Hz	80% RMT	300	N. S.
Avanzino et al., 2008 [67]	1 Hz	90% RMT	1200	Hasten movement speed (externally-paced finger tapping)

Table 5. High-frequency and patterned rTMS over ipsilateral M1 and motor control.

Authors and year	Stimulus frequency	Stimulus amplitude	Total number of pulses	Significance in motor parameters (N. S. means no significance)
figure of eight coil, during movement			Time for interfering	
Chen et al., 1997 [40]	15 Hz	120% RMT	2.3 seconds	Increase timing errors in sequential movement, especially in complex sequence. Disturbing even after stimulus with complex sequence in the left side
cTBS				
Huang et al., 2005 [20]	5 Hz	80% AMT	300	Shorten reaction time at 30 minutes after TBS
Stefan et al., 2008 [51]	5 Hz	70% RMT	300	N. S.

function elicited more disturbances in ipsilateral sequential finger movement, especially for complex motor programs. In contrast, delivering 150 pulses of sub-threshold 5-Hz rTMS (90% AMT) over M1 did not change the control of ipsilateral finger tapping force [45].

3.3 Theta burst stimulation

Research has shown that cTBS300 (80% AMT, 300 pulses) shortened the simple choice reaction time of the ispilateral index finger at 30 minutes after cTBS300 [20]. It looks likely that such improvement in the reaction time is due to a learning effect. A similar effect was not observed in the contralateral hand, perhaps indicating that conditioning with cTBS not only affected reaction time, but also motor learning. It is possible that the hypofunction of the cTBS-conditioned hemisphere produced a reciprocal hyperfunction of the unconditioned hemisphere. The reciprocal hyperfunction could facilitate motor responses in the unconditioned ipsilateral hand via a similar mechanism to that observed in human subjects following unilateral stroke [61]. In contrast, Stefan et al. reported that modified cTBS300 (70% RMT, 300 pulses) directed to ipsilateral M1 did not alter the force production performance [51].

cTBS has been practiced on the unaffected M1 in chronic stroke patients [68]. Distinct from the low-frequency rTMS on the unaffected hemisphere, the inhibitory cTBS300 (80% AMT, 300 pulses) could not improve motor capacity in the paretic hand, despite a significant suppression of corticospinal excitability in the unaffected side.

4. Discussion

The effects of varied rTMS protocols on motor control can be categorized into three groups, low-frequency, high-frequency and patterned rTMS over M1 contralateraal or ipsilateral to the moving limb.

4.1 rTMS protocols and motor performance

Table 1 lists the responses to different protocols of low-frequency rTMS over contralateral M1. Although the results are inconsistent and sometimes confusing, low-frequency rTMS tends to slow down the motor performance and worsen the motor learning. The interference of motor learning occurs 'off-line' which can hardly be seen immediately after rTMS. In contrast, it is required to give rTMS within a certain time window after motor training to eliminate the learning effect. However, it is difficult to have a conclusive answer on the choice of protocols. There is a trend that sub-threshold low-frequency rTMS with more lengthy stimulation is more potential to have a behavioral effect. During movements, a short train of high-frequency rTMS over contralateral M1 clearly interferes the motor executions (Table 2) [40-42]. However, the after-effect of a longer train of high-frequency rTMS is less consistent, and only some improvement in the motor performance has been shown so far.

The inhibitory cTBS affects motor performance more profoundly than the low-frequency rTMS. Huang et al. depicted that cTBS significant reduces the motor performance in the contralateral index finger (Table 3) [20]. The inhibitory nature of cTBS also projects on the force generation [51]. Due to the inhabitation of the cortical excitability, the precision of force control was impaired. However, the behavioral effect of paired-pulse rTMS was less investigated and not conclusive.

The motor performance after ipsilateral low-frequency rTMS tends to accelerate movement speed [26,29,67], although similar rTMS protocols produced opposite results in few studies [28] (Table 4). The contradictory responses could be explained by varied cortical mechanism in controlling different tasks (externally-paced vs. self-paced finger movements) [67]. The effect of ipsilateral high-frequency rTMS on the motor performance has been rarely explored (Table 5). Research has shown that cTBS accelerates the motor response in the ipsilateral index finger [20].

Concerning the MEP responses to rTMS, the behavioral modulations after M1 stimulation are analogous to the cortical excitability changes. When applied over M1, low-frequency rTMS and cTBS tend to decelerate the contralateral movement [28,32] and accelerate the ipsilateral movement [19]. On the contrary, high-frequency rTMS is prone to accelerate the contralateral movement [27,46], while the effect on ipsilateral performance was less explored.

4.2 The inconsistency and variability between studies

The current review demonstrated that modulating cortical neuronal excitability via ipsilateral or contralateral M1 stimulation among healthy subjects does not necessarily ensure changes in the motor performance or in sequence of motor learning. In addition, the results among different studies have been inconsistent. The discrepancies could be due to (1) different protocols and motor tasks, (2) poor effectiveness of rTMS and (3) compensation through complicated neural network.

Looking into the details of the experimental paradigms, the stimulation protocol has been varied among studies. In particular, very different stimulus intensity range from 80% AMT to 125% RMT and very wide range of pulse number (from few to 1800 pulses) have been used in conventional rTMS. In addition, different motor tasks were used in different studies, although some were very similar. It is believed that these are the major causes for the inconsistent results of rTMS effects on motor performance. However, we cannot ignore another possibility that the poor effectiveness of rTMS produced such variable results. Although low-frequency and high-frequency rTMS have shown inhibition and facilitation in corticospinal excitability, these modulation effects have been known to be unstable and inconsistent [69]. It is expected that the newly developed patterned rTMS, e.g. TBS, paired-pulse rTMS, provide better paradigms for testing the facilitory and hinbitory effects to reach conclusive results in the near future.

However, a more powerful protocol may not promise to produce a profound effect on the motor performance. Brain is a very complicated network and the network maintains comprehensive communications between areas. The primary motor cortex never works alone and always keeps communicating with other areas in the brain throughout the movement sequence. Modulating the activity of motor cortex inevitably affects the coordination inside the motor network and induces remote effects in other areas. The remote compensatory activities in other areas could maintain the behavior unchanged. This is supported by imaging studies showing acute functional remapping in the motor system after rTMS [31,70-72]. The concept of neuronal "network" which governs motor control and learning can never be overemphasized.

5. Conclusions

Delivering rTMS over the primary motor cortex produces local and distant changes of neuronal activities in the motor system and results in modulation of motor control and learning. However, the results have been weak and inconsistent so far. The newly developed patterned rTMS and further concise understanding of the interaction within the motor network would be helpful to elucidate the effect of rTMS on motor performance and to clarify the function of primary motor cortex.

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