

TOPICAL REVIEW

Using repetitive transcranial magnetic stimulation to study the underlying neural mechanisms of human motor learning and memory

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In the last two decades, there has been a rapid development in the research of the physiological brain mechanisms underlying human motor learning and memory. While conventional memory research performed on animal models uses intracellular recordings, microfusion of protein inhibitors to specific brain areas and direct induction of focal brain lesions, human research has so far utilized predominantly behavioural approaches and indirect measurements of neural activity. Repetitive transcranial magnetic stimulation (rTMS), a safe non-invasive brain stimulation technique, enables the study of the functional role of specific cortical areas by evaluating the behavioural consequences of selective modulation of activity (excitation or inhibition) on memory generation and consolidation, contributing to the understanding of the neural substrates of motor learning. Depending on the parameters of stimulation, rTMS can also facilitate learning processes, presumably through purposeful modulation of excitability in specific brain regions. rTMS has also been used to gain valuable knowledge regarding the timeline of motor memory formation, from initial encoding to stabilization and long-term retention. In this review, we summarize insights gained using rTMS on the physiological and neural mechanisms of human motor learning and memory. We conclude by suggesting possible future research directions, some with direct clinical implications.

(Received 18 August 2010; accepted after revision 29 October 2010; first published online 1 November 2010)

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The human brain has remarkable capabilities to improve motor performance with practice. Repetitive transcranial magnetic stimulation (rTMS) has become a widely used, safe (Wassermann, 1998; Rossi *et al.* 2009) non-invasive technique that applied to discrete brain areas can help identify neural substrates of human motor learning and

memory. By evaluating the behavioural consequences of disruption of activity in specific cortical regions with rTMS, it is possible to identify a cause–effect link between such activity and function, a powerful approach which complements brain imaging studies (Reis *et al.* 2008).

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TMS operates by creating a pulse magnetic field, which induces focal current flow and neural activation in the targeted cortical brain area (Hallett, 2005). Recently, it has been proposed that rTMS can stimulate deeper brain areas as well (Zangen *et al.* 2005). If reproduced, this approach may have an important impact on future research, further contributing to the study of the involvement of subcortical regions in motor learning. Single pulse TMS has been an important tool to study the mechanisms of motor learning and memory as reviewed before (see for example Bütefisch *et al.* 2004; Hadipour-Niktarash *et al.* 2007). Here, we will focus on the unique contribution of rTMS to the understanding of these mechanisms. Generally, low-frequency rTMS (i.e. 1 Hz) induces inhibitory effects on motor cortical excitability allowing creation of a reversible 'virtual lesion' (Chen *et al.* 1997). This approach, somewhat resembling 'gene knockout' in genetic research (though the direct effects induced by rTMS are temporal and reversible), enables the functional role of the specific targeted brain area on motor learning to be studied. High-frequency rTMS (5–20 Hz) usually increases cortical excitability (Pascual-Leone *et al.* 1994; Beradelli *et al.* 1998). We will not discuss other invasive or non-invasive brain stimulation techniques, addressed in previous reviews (see for example Reis *et al.* 2008; Bolognini *et al.* 2009).

Motor learning and memory

The brain is constantly changing in response to environmental challenges. Training leads to learning of visual-perceptual (Karni & Sagi, 1993; Stickgold *et al.* 2000; Fahle, 2004; Censor *et al.* 2006) and motor (Brashers-Krug *et al.* 1996; Walker *et al.* 2002; Korman *et al.* 2003; Robertson *et al.* 2004) skills. Improving motor functions through efficient practice has an important impact on daily living activities of healthy subjects as well as patients with neurological disorders. Memories acquired during practice may be strengthened through consolidation after training finished. Such offline improvements in performance have been shown in the framework of different skill types, with studies showing that sleep plays an important role in strengthening of motor memories (Walker *et al.* 2002; Korman *et al.* 2007). rTMS enables the study of the mechanisms underlying consolidation (see Fig. 1), which refers to the process by which acquired memories become stable or strengthened over time and resistant to interference by chemical, electrical or behavioural interventions (Brashers-Krug *et al.* 1996; McGaugh, 2000; Dudai, 2004). Reactivation of previously consolidated memories turns them transiently labile to subsequent degradation, stabilization or further strengthening, a process referred to as reconsolidation (Walker *et al.* 2003; Dudai & Eisenberg, 2004; Stickgold

& Walker, 2005; Nader & Hardt, 2009; Censor *et al.* 2010). Applying rTMS during reactivation of a motor memory enables the mechanisms underlying reconsolidation to be studied (Censor *et al.* 2010, see Fig. 1). One of the important features of rTMS has been its exquisite time resolution. Therefore, it is possible to apply rTMS at different stages during the preparation, execution and consolidation of a memory. Evaluation of the behavioural consequences of focal disruption or facilitation of excitability at each stage provides the opportunity to study specific spatiotemporal patterns of involvement of cortical areas associated with learning.

Primary motor cortex

Consolidation and resistance to interference. Following their initial acquisition through training, motor skills are consolidated into a more stable state, resistant to interference (Brashers-Krug *et al.* 1996). Muellbacher and colleagues (2002) applied 15 min of 1 Hz rTMS over the primary motor cortex (M1) immediately following practice of a ballistic finger movement task, which disrupted the retention of behavioural improvements as opposed to stimulation of other control brain areas. When rTMS to M1 was applied 6 h after practice, retention of the newly acquired motor skill was not disrupted. These results demonstrated that M1 is specifically engaged during the early stage of motor memory consolidation and are in line with psychophysical studies, showing that an acquired motor memory becomes resistant to interference several hours after practice (Brashers-Krug *et al.* 1996). Another study (Baraduc *et al.* 2004) has replicated these results and additionally showed that rTMS had no effect on retention of dynamic force-field adaptation. Therefore the authors suggested that unlike the learning of simple ballistic tasks, the learning of dynamics may be stored outside M1 in a more distributed manner. Interestingly, learning a motor task by observation has also been shown to rely to some extent on M1 function since rTMS to M1 is capable of disrupting it (Brown *et al.* 2009) consistent with previous reports of its involvement in this task (Stefan *et al.* 2005). These findings raised the question of possible different roles of M1 in consolidation of different forms of learning.

Consolidation and off-line gains in performance. In addition to the definition of a consolidated memory as one that implies resistance to interference as described above, consolidation has also been referred to as memory improvements that take place after the end of the training session (off-line gains, Walker *et al.* 2002; Korman *et al.* 2007). An interesting study by Robertson and colleagues (2005) has shown that 1 Hz rTMS of M1 applied immediately following practice of a sequential serial reaction time task (SRTT) blocks off-line improvements over the day but not overnight. This study suggested that

different mechanisms and possibly brain areas are engaged during daytime and during overnight consolidation (as evident by differential effects on off-line gains), the latter involving an additional brain-state of sleep. Implicit and explicit motor sequence learning are influenced by sleep in different manners. It was shown that while explicit off-line learning is sleep dependent and correlates with the amount of non-rapid eye movement, implicit off-line learning does not depend on sleep (Robertson *et al.* 2004). As an example, the amount of slow wave sleep correlated with the learning of a visuomotor rotation adaptation task (Huber *et al.* 2004). It has been proposed that slow oscillations during sleep may produce synaptic downscaling and an increase in signal-to-noise ratios in the relevant trained neural circuits allowing improved performance (Tononi & Cirelli, 2003). Another study (Hotermans *et al.* 2008) has shown that rTMS to M1 immediately before testing an explicit finger-tapping task disrupts only the early off-line improvements (30 min after practice) but not the delayed off-line gains (observed 48 h later). rTMS has also been used in order to study learning of movement dynamics in adaptation paradigms, showing that 1 Hz disruption of M1 for 15 min immediately before learning reaching movements in a force field does not impair performance in the learning epoch itself but rather in the re-test of the following day (Richardson *et al.* 2006). Therefore it was suggested that M1 function contributes substantially to the early stages of memory consolidation (see also Cothros *et al.* 2006). On the other hand, Iezzi *et al.* (2010) have shown that inhibitory continuous theta-burst stimulation (cTBS, see Huang *et al.* 2005) over M1 interferes with early

motor learning and retention of a finger movement task, but does not interfere with consolidation measured on the day following practice. Such differences between studies may arise from the use of different rTMS techniques and types of motor tasks (Iezzi *et al.* 2010).

Reconsolidation. A recent study (Censor *et al.* 2010) has shown that 1 Hz rTMS applied to M1 during reactivation of an already consolidated motor memory consisting of an explicit finger-tapping sequence blocks further memory modification (reconsolidation). In addition to animal studies proposing models according to which reactivated memories may be modified while being temporarily in their active state (Lewis, 1979; Nader & Hardt, 2009), the results of this study enabled the authors to suggest a model for human motor memory modification. The model differentiates between an executing storage domain (M1) which upon memory reactivation interacts with the environment and updates the core storage domain, which may include the cerebellum, striatum and/or other motor-related cortical areas and the hippocampus (shown to be involved in the generation of procedural memories, Shadmehr & Holcomb, 1997; Doyon *et al.* 2002; Albouy *et al.* 2008; Debas *et al.* 2010).

Non-primary motor cortices

Non-primary motor areas and the cerebellum are strongly involved in skill acquisition. The cerebellum contributes to the timing of motor movements (for example externally

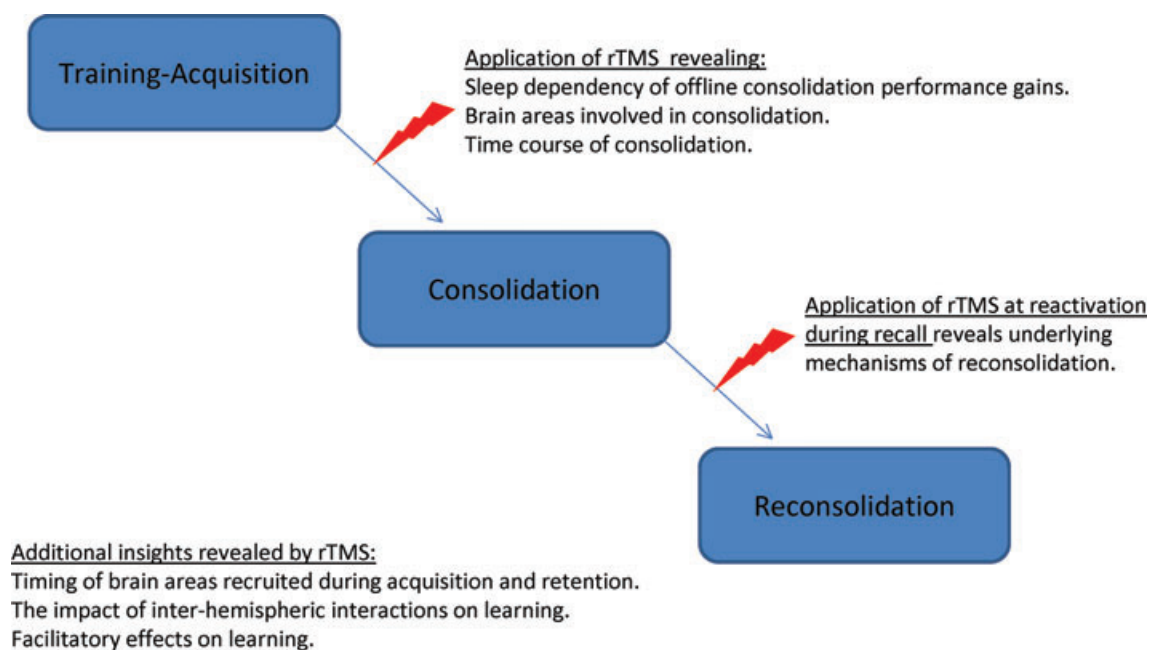


Figure 1

Schematic illustration summarizing some uses of rTMS in motor learning and memory research.

paced rhythmic movements of the right index finger, Del Olmo *et al.* 2007): a transient virtual lesion using 1 Hz rTMS of the cerebellum ipsilateral to the movement in a finger-tapping task or of the contralateral premotor cortex results in an increase in the variability of the inter-tap interval but only for movements at 2 Hz. These data have been interpreted as indicative of the involvement of a cerebellar-premotor network in event-related timing in the subsecond range (Del Olmo *et al.* 2007).

Other studies demonstrated that disruption of activity with 5 Hz rTMS applied over the right dorsolateral prefrontal cortex (DLPFC) resulted in impairments in procedural learning (Pascual-Leone *et al.* 1996). On the other hand, supporting the hypothesis that declarative and procedural consolidation processes interfere with each other under certain conditions (Brown & Robertson, 2007*a,b*), Galea and colleagues demonstrated that intermittent theta-burst stimulation (iTBS, see Huang *et al.* 2005) over DLPFC lead to offline daytime improvements in the SRTT (Galea *et al.* 2010). rTMS over DLPFC may also interfere with performance of a visuomotor task containing a sequence to which subjects were previously exposed by observational learning, whereas rTMS applied over the cerebellum interfered with the performance of a newly presented sequence (Torriero *et al.* 2007).

rTMS studies unveiled the involvement of the supplementary motor area (SMA) in intermanual transfer of procedural motor learning (Perez *et al.* 2008) and in processes leading to successful motor memory recall, dependent on practice structure (Tanaka *et al.* 2009), which may also rely to some extent on DLPFC function (Kantak *et al.* 2010). Interestingly, it has been shown that 1 Hz rTMS over the primary somatosensory cortex (S1) reduces the magnitude of motor learning by reducing performance accuracy in a visuomotor tracking task (Vidoni *et al.* 2010). These findings are intriguing given the scarcity of reports in humans trying to separate the involvement of M1 and S1 in motor learning, an issue extensively explored in animal models. In one of these rTMS reports, it was demonstrated that M1 contributes to anticipatory grip-force scaling while S1 contributes to object manipulation in a precision grasping task (Schabrun *et al.* 2008).

Various motor tasks and practice schedules have been investigated in motor learning and memory research. rTMS enables the dissociation of the different brain mechanisms involved, which depend on practice type and schedule. For example, Tanaka and colleagues (2009) have shown that 1 Hz rTMS over SMA following block-designed training of a motor task reduced recall performance compared to sham and SMA stimulation applied 6 h after training, pointing to the involvement of SMA in motor memory consolidation. However, most interestingly, the study showed that when the same stimulation procedure was applied following random

practice, there was no effect on recall, posing the hypothesis of an earlier involvement of this region in consolidation taking place as training evolved. The involvement of M1 in motor memory consolidation has also been shown to depend on practice type, with M1 being more involved in constant, repetitive-based learning (Karni *et al.* 1995; Classen *et al.* 1998; Bütefisch *et al.* 2000; Kantak *et al.* 2010). On the other hand, it has been proposed that error-based learning relies to a larger extent on cerebellar function (Tseng *et al.* 2007). Such studies show that the brain mechanisms underlying motor learning and memory highly depend on practice type and structure (see also Diedrichsen *et al.* 2010).

Timing of rTMS

The brain areas recruited during skill acquisition vary depending on the exact timing relative to performance of the training movements. rTMS has been used to study intermanual transfer of motor learning, defined as performance improvements in an untrained hand with training of the opposite hand (Perez *et al.* 2007*b*). Previous functional magnetic resonance imaging (fMRI) work documented activation of the SMA with successful intermanual transfer (Perez *et al.* 2007*a*). To evaluate the extent to which SMA activity actually contributed to successful transfer, rTMS was used to induce a transient virtual lesion of the SMA during training. Perez and colleagues (2008) showed that there was less intermanual transfer of learning when stimulation was applied at the premovement phase of training motions, compared to rTMS application in the movement phase or with sham stimulation. Studies like this document a direct causal link between the timing of activity in specific brain areas and specific stages of motor learning and memory processes.

As mentioned above, the importance of the exact timing at which rTMS is applied was also shown with regard to the cerebellum, with studies pointing to the involvement of the cerebellum in the timing of motor movements such as finger tapping (Del Olmo *et al.* 2007). Additionally, retention of visuomotor skills such as adaptation of arm movements to a visuomotor rotation was shown to depend on the exact timing at which M1 was disrupted (Hadipour-Niktarash *et al.* 2007).

Interaction between hemispheres

rTMS has been used to study interactions between right and left motor cortices and the impact of such interaction on motor learning. 1 Hz rTMS applied to M1 improved the performance of a sequential finger movement motor task when performed with the ipsilateral hand and was associated with increased intracortical excitability of the unstimulated M1 (Kobayashi *et al.* 2004, 2009;

Schambra *et al.* 2003), possibly by releasing it from transcallosal inhibition by the stimulated M1. Furthermore, excitability changes in the ipsilateral M1 were shown to compensate for contralateral M1 dysfunction induced by rTMS (Strens *et al.* 2003). Other studies have used rTMS to explore cross-limb transfer of learning (Lee *et al.* 2010). An interesting approach for studying interhemispheric interactions using rTMS was introduced by Chiang and colleagues (2007) who used near infrared spectroscopy to show that the level of oxyhaemoglobin in the unstimulated M1 increased after 20 min of 1 Hz rTMS over the contralateral hemisphere, an increase which lasted 40 min after stimulation.

Beyond the knowledge gained by such studies regarding how the two motor cortices interact to produce motor output and motor learning, these studies provided a basis for the development of interventional approaches to ameliorate motor disability after stroke, presently under investigation (Floel *et al.* 2008).

Facilitatory effects of high-frequency rTMS

TMS application may result in increased corticomotor excitability (Pascual-Leone *et al.* 1994; Beradelli *et al.* 1998) as well as motor cortical plasticity in healthy subjects (Bütefisch *et al.* 2004). In healthy subjects, high-frequency rTMS applied just prior to the beginning of a sequential finger-tapping motor task enhanced the learning of a motor sequence compared to sham stimulation (Kim *et al.* 2004). In contrast, some studies have shown that despite this increase in cortical excitability of M1, neither subthreshold 5 Hz rTMS nor iTBS improved either motor performance or learning associated with rapid repetitive index finger abduction motions (Agostino *et al.* 2007, 2008) or synchronized co-contraction of the right abductor pollicis brevis and deltoid muscle compared to sham stimulation (Sczesny-Kaiser *et al.* 2009). These reports led to the proposal (Sczesny-Kaiser *et al.* 2009) that different motor tasks are affected differently by high-frequency rTMS to M1, with some motor tasks being more dependent on processing in non-primary cortical areas like the premotor cortex, posterior-parietal area and basal ganglia (Catalan *et al.* 1998; Mima *et al.* 1999). More importantly, they raised awareness that prediction of TMS effects on behaviour cannot be automatically extrapolated from its effects on motor cortical excitability.

High-frequency rTMS applied over the dorsal premotor cortex (PMd) elicited off-line gains in performance of a visuomotor tracking task compared to 1 Hz or sham stimulation under which no off-line gains were documented (Boyd & Linsdell, 2009). These findings support the hypothesis that PMd contributes to motor learning and off-line consolidation. It is important to note that the effects of high-frequency rTMS do not seem to be limited only to the motor domain, with studies showing

that 5 Hz rTMS applied over the cortical representation of the right index finger of S1 improves tactile discrimination. Furthermore, fMRI showed that this stimulation resulted in larger representation of the right index finger in S1 (Tegenthoff *et al.* 2005).

In patients with stroke, it has been proposed that high frequency rTMS over the ipsilesional M1 could facilitate motor cortical excitability and motor performance in patients with chronic stroke (Kim *et al.* 2006, but see also Talelli & Rothwell, 2006).

Conclusion and future directions

rTMS studies over the last decade provided important insights into the mechanisms of motor learning and memory formation. In its inhibitory or excitatory forms, rTMS has been utilized to evaluate neural substrates of different stages of motor skill learning in health and disease. Proof of principle studies suggest that facilitating excitability in the ipsilesional motor cortex after brain lesions like stroke or inhibiting the unaffected motor cortex may improve motor performance, a hypothesis presently evaluated as an adjuvant to training-based rehabilitation protocols (Ward & Cohen, 2004; Khedr *et al.* 2005; Kim *et al.* 2006; Fregni *et al.* 2006; Talelli *et al.* 2007; Takeuchi *et al.* 2008; Emara *et al.* 2010) but larger well-controlled multicentre clinical trials are required before firmer conclusions on clinical usefulness can be drawn.

An additional exciting avenue for future research is the use of rTMS in the setting of multimodal investigations that include also functional and anatomical neuroimaging (O'Shea *et al.* 2007), electroencephalography (Hamidi *et al.* 2010), and positron emission tomography (Eisenegger *et al.* 2008; Conchou *et al.* 2009). Such combinations could be used in various ways, for example by applying rTMS and then exploring the reorganization of the stimulated or distant brain regions using techniques such as fMRI. It is also possible to identify the neural structures activated in association with a particular form of learning and then determine the behavioural consequences of rTMS application, which provides a cause-effect link between activation and function.

In summary, rTMS is already a heavily used technique in the study of mechanisms and modulation of motor skill learning. It is likely that future investigations will continue providing important information in this regard with meaningful clinical implications.

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