

Consolidation of Dynamic Motor Learning Is Not Disrupted by rTMS of Primary Motor Cortex

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Summary

Motor skills, once learned, are often retained over a long period of time. However, such learning first undergoes a period of consolidation after practice. During this time, the motor memory is susceptible to being disrupted by the performance of another motor-learning task [1, 2]. Recently, it was shown that repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex could disrupt the retention of a newly learned ballistic task in which subjects had to oppose their index finger and thumb as rapidly as possible [3]. Here we investigate whether the motor cortex is similarly involved during the consolidation that follows learning novel dynamics. We applied rTMS to primary motor cortex shortly after subjects had either learned to compensate for a dynamic force field applied to their index finger or learned a ballistic finger abduction task. rTMS severely degraded the retention of the learning for the ballistic task but had no effect on retention of the dynamic force-field learning. This suggests that, unlike learning of simple ballistic skills, learning of dynamics may be stored in a more distributed manner, possibly outside the primary motor cortex.

Results

We used two tasks to assess the effect of repetitive TMS on M1 during the consolidation phase of motor learning. Subjects participated in two sessions of either a ballistic-movement (BM) experiment or a force field (FF) learning experiment with their left or right hand. In between the two sessions, 15 min of repetitive transcranial magnetic stimulation (rTMS) or sham rTMS (SHAM) was performed over the primary motor cortex (See Experimental Procedures for details).

Force Field Training

Subjects were required to move their index finger toward targets, at first without any force applied to the finger

and then in a novel force field (FF) generated by a robot (Figure 1A). Initial exposure to the force field produced large deviations of the finger trajectory from the desired straight-line path (Figure 1B left; Figure 2, difference between baseline no-force phase and preTMS phase). These deviations progressively decreased as learning proceeded, both for groups who used their left (Figure 2A, preTMS phase) index finger and those who used their right (Figure 2B, preTMS phase). At the end of this preTMS phase, the late preTMS deviations were significantly less than the early preTMS deviations (ANOVA, $p = 0.0015$ for the period effect in the FF-L/rTMS and $p = 0.028$ FF-R/rTMS). After the rTMS period, subjects resumed the task with no deterioration of performance. Comparison with the sham rTMS groups showed that the error peak on the first postTMS block was solely an effect of the period of inactivity (nonsignificant difference between first postTMS block deviations SHAM and rTMS, $p = 0.63$ for FF-L and $p = 0.40$ for FF-R). Overall, early postTMS deviations (second and third blocks after TMS) did not differ significantly from the late preTMS deviations for the FF-L/rTMS group (paired t test, $p = 0.18$) and were significantly lower for FF-R/rTMS (paired t test, $p = 0.0013$). This was confirmed when a target-by-target analysis of late preTMS against early postTMS found no effect of rTMS (paired t tests, all but one $p > 0.14$ for FF-L/rTMS, all $p > 0.18$ for FF-R/rTMS); on one occasion there was a significant performance improvement ($p = 0.02$ for target 2 in FF-R/rTMS). Moreover, although an effect of the target was significant in FF-R/rTMS (ANOVA $p = 0.025$), there were no consistent differences between targets in regard to the effect of rTMS. In particular, there was no relationship between the pulling direction of FDI and the effectiveness of rTMS. In all groups, true learning took place, and the improvement in performance was not solely due to an increase in finger stiffness; performance in final catch trials deviated significantly more from a straight-line path than in the no-field late baseline phase (ANOVA, $p = 0.0025$ for period effect in FF-L/rTMS; $p = 0.034$ for FF-R/rTMS).

Ballistic Training

Separate groups of subjects were trained at a ballistic-movement (BM) task, in which they were requested to produce a rapid ballistic finger abduction so as to achieve the highest initial acceleration possible. During the preTMS phase, initial acceleration progressively increased by a factor of more than 2 (Figures 3A and 3B). Late preTMS acceleration was significantly higher than early PreTMS acceleration (t test, $p = 0.003$ for BM-L/rTMS, $p = 0.048$ for BM-R/rTMS). In contrast to the force field/rTMS groups, rTMS induced a significant degradation of performance for the left hand (difference between late preTMS and early postTMS, $p = 0.008$). The effect of the training was almost completely abolished, and early postTMS acceleration was not significantly different from early preTMS acceleration ($p = 0.17$). However,

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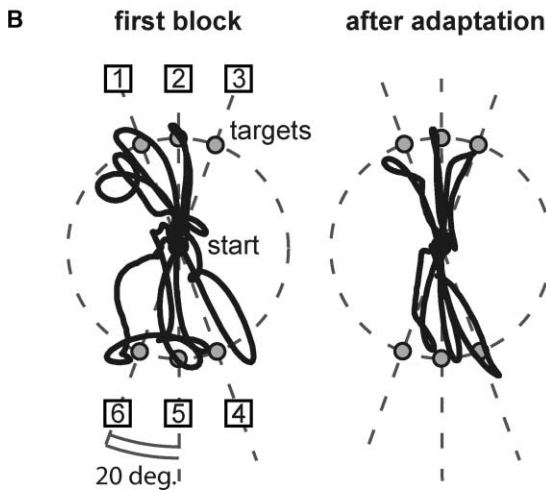
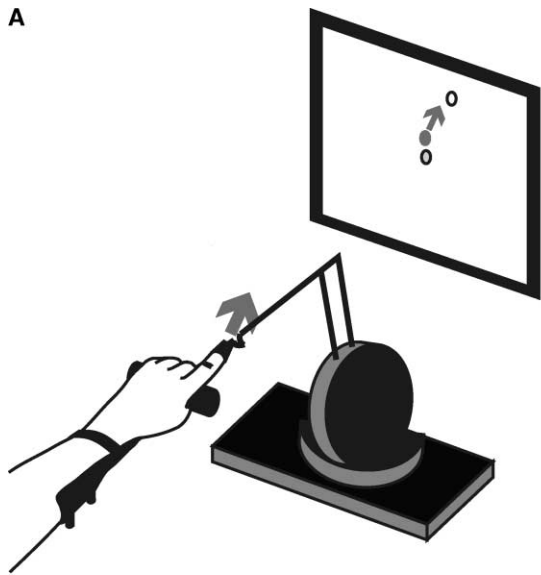


Figure 1. Motor-Learning Task

(A) Experimental setup. The subjects gripped a horizontal bar while their arm was immobilized in a modified brace. The fingertip was held by a robot that recorded its motion and exerted a force dependent on the fingertip's position and velocity (force field experiments only, see Experimental Procedures). Finger motion, as well as the starting location and the target, was displayed on a monitor in front of the subject.

(B) A subject's typical fingertip trajectories for their left index finger to the six targets (gray discs), in the first block of learning and in a later block when asymptotic performance was reached. Only one target was used in the ballistic movement task to cause an abduction movement (target and trajectories not shown). Boxes specify target numbers.

this did not impair subjects' learning ability because performance levels rose again to late preTMS levels (no difference between late preTMS and late postTMS, $p = 0.27$). Sham rTMS did not produce a similar decrease in performance, and there was no significant difference between late preTMS and early postTMS ($p = 0.34$).

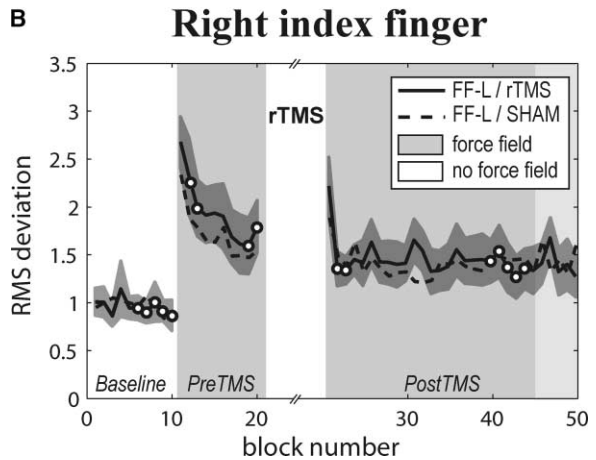
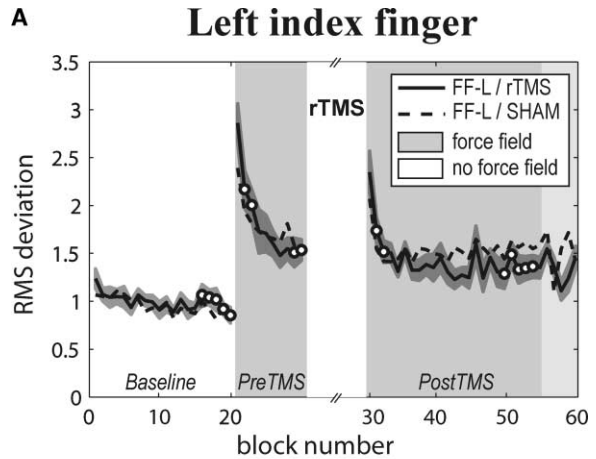


Figure 2. RMS Movement Deviation from the Straight Line as a Function of Block Number for the Force Field Learning Experiment (A) Left-handed groups, rTMS group (solid), and sham rTMS group (dashed).

(B) Right-handed groups. A gray background indicates blocks in the presence of the force field (light gray: mix of force field and catch trials). Shaded area: mean \pm SE. Circles denote blocks considered for statistical analysis: late baseline, early preTMS, late preTMS, early postTMS, and late postTMS periods.

For the right-hand experiments, we found a similar but nonsignificant decrease after rTMS ($p = 0.13$; subjects had not reached a similar late preTMS skill level). As expected, sham rTMS produced no effect ($p = 0.20$).

Discussion

We have confirmed findings by Muellbacher et al. [3] that early motor consolidation after ballistic training of a muscle or group of muscles (here primarily FDI) is disrupted by a period of 15 min rTMS over the corresponding region in M1 (BM-L/rTMS). However, in stark contrast, the learning of a novel external force field remained unaffected by the same cortical stimulation (FF-L/rTMS and FF-R/rTMS). This suggests that the consoli-

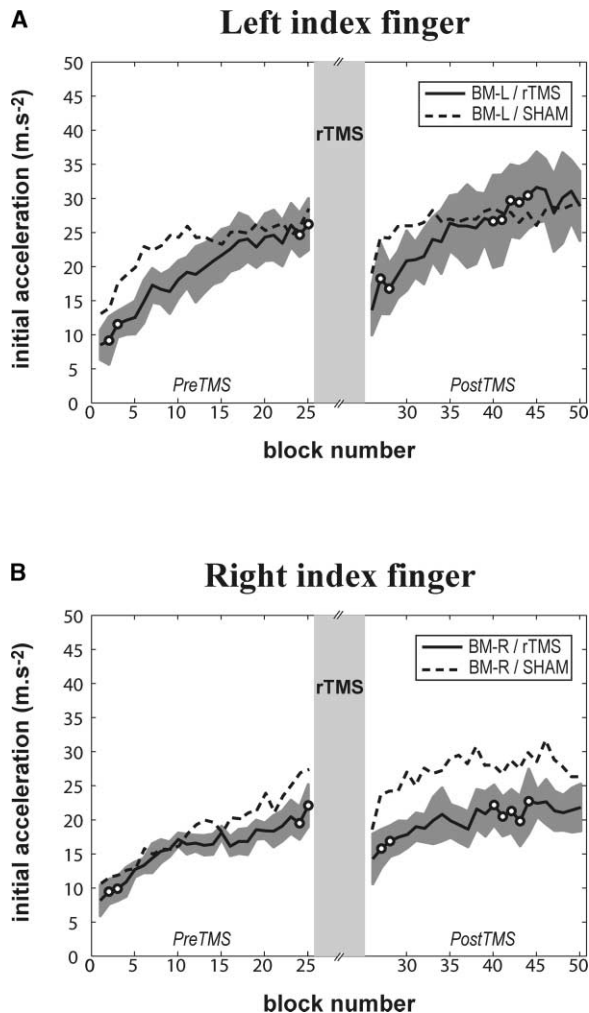


Figure 3. Initial Acceleration as a Function of Block Number for the Ballistic Movement Task

(A) Results for the left-handed group, with rTMS (solid) and sham rTMS (dashed).

(B) Results for the right-handed groups. The same graphical conventions were used as in Figure 2.

ation of dynamic motor learning can be dissociated from the consolidation of basic muscular training.

The force field task involves more muscles than just the FDI, and it could be argued that focal rTMS is insufficient to affect global performance. However, a similar argument could be applied to the ballistic task. Moreover, although movement to the six targets involved FDI differently, performance level was not differentially affected by rTMS. In particular, movements starting with abduction should have been more affected by the stimulation, which was not observed. Thus, it is unlikely that rTMS induced any modification to the projections to FDI that could affect motor coordination.

There are two main reasons that could give rise to the difference in the effects of rTMS on the consolidation of the two motor tasks. First, the memory of the motor training in the ballistic and force field tasks could be stored in M1, but in a different manner for each task. The substrate for memory in the BM task could be more

likely to be disrupted by rTMS than that for motor memory of the FF task. Alternatively, the motor engrams for the force field task could be distributed over several cerebral areas. We will now discuss each of these hypotheses.

Ballistic versus Force Field: Different Memories in M1?

Repetitive training of a single ballistic movement has been shown to transiently modify corticospinal excitability so as to favor a particular pattern of motor output [4]. The cellular bases of this modification are unknown. However, practicing a ramp pinch (as opposed to a ballistic one) does not lead to measurable changes in corticospinal excitability [5]. We speculate that the effect observed in the ballistic tasks might be due to the increased recruitment of specific corticospinal projections, for instance through an increase in excitability of all neurons that have no inhibitory inputs to the target muscle as well as no excitatory inputs to its antagonists. Accordingly, the effect of rTMS on the ballistic task would be very specific to the generation of a synergic activity burst, and no generic conclusions about motor learning could be drawn.

In contrast to the ballistic task, in the force field task a simple modification of M1 outflow would not be enough to improve performance because it does not require a force burst but rather a precisely coordinated muscle activity (in our view, this feature of the FF task makes it a more attractive model of motor learning). It is possible that the neural bases of this learning in the motor cortex substantially differ from those involved in force burst training. It could also be that key features of the force field learning are insensitive to rTMS. In particular, it is unclear whether a global lowering of cortical excitability by rTMS can substantially affect the timing of the neuronal discharge, which is crucial to the execution of the FF task. These factors or combination of factors could explain why the FF task is less susceptible or not at all susceptible to disruption by rTMS. Further investigation of the post-rTMS excitability changes induced by rTMS and their correlation with task performance indices would help shed light on this issue.

Force Field Task: Consolidation outside M1?

The second possibility is that consolidation of the dynamic task happens at least partially outside M1 in the FF task. Animal studies of visuomotor learning have highlighted the role of the supplementary motor area [6], premotor cortex [6–8], parietal cortex [9], and cerebellum [10, 11]. More specifically, monkeys learning new dynamics show lasting changes of neuronal tuning not only in M1 [12] but also in SMA [13]. Functional imaging studies in humans have confirmed that all the previously mentioned structures and the basal ganglia are activated during skill learning [14–18]. In particular, several PET studies have highlighted regions that are specifically active during the early learning phase, independently of motor performance. Consistently activated were the thalamus/basal ganglia [15] and the dorsolateral prefrontal cortex [14, 18]. Whether these structures participate in learning or in its early consolidation is

unclear. Alternatively, it has been proposed that learning the dynamics of a new tool leads to the formation of an internal model [19], which could be stored in the cerebellum, as suggested by experimental [11, 16, 20] as well as theoretical studies [21, 22]. However, testing this theory with TMS would be difficult because of the distance between the cerebellar cortex and the neck surface. Besides, adaptation to force fields is partially independent of the effector [23], which suggests that a nonmotor memory of the force field properties exists. In which cerebral structure(s) this nonmotor memory is consolidated and whether application of rTMS on them would significantly suppress the learning effects remain open questions.

Conclusions

We have shown here that learning to make ballistic movements of the finger and learning novel finger dynamics are tasks that are differentially affected by repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex. This indicates that the motor memory of these two tasks is of a different kind, the memory of novel dynamics being possibly more distributed.

Experimental Procedures

Subjects

Thirty-eight right-handed subjects (nine females, 29 males, age 18–36) naive to the purpose of the experiment gave written informed consent and participated in this study. Subjects reported no history of neurological disorders and no contraindication to TMS [24]. All experiments were designed to assess the effect of repetitive TMS on M1 during the consolidation phase of motor learning. Subjects either participated in a ballistic-movement (BM) experiment or in a force field (FF) learning experiment by using either their left (FF-L and BM-L) or right (FF-R and BM-R) hand. Subjects either received rTMS (TMS groups) or Sham rTMS (SHAM groups), making 8 groups in total. Five subjects participated in each BM group that received TMS, and four participated in each associated SHAM group. Seven subjects participated in each FF-L group (rTMS and SHAM), and five participated in each FF-R group.

Force Field Experiments

Subjects' right (group FF-R) or left (group FF-L) forearm rested on a modified brace with the wrist attached to the brace with a strap. The hand gripped a horizontal bar fixed at the distal end of the brace. The index finger was attached to the extremity of a Phantom Haptic Interface 1.5 (SensAble Technologies, Woburn, Massachusetts) that was also used to record movement kinematics at 200 Hz and generated forces on the finger. Subjects were requested to make a quick, straight there-and-back movement from a center starting position toward one of six targets by using a combination of abduction/adduction and flexion/extension of the metacarpophalangeal joint of their index finger. For increased accuracy, visual feedback of the fingertip's position was magnified $2.4\times$ and presented on a screen in front of the subjects. Movement time was constrained to be under 175 ms, and a buzzing tone and a background color change signaled movements that exceeded this time. Targets were presented in pseudorandom order. After a familiarization period to ensure that subjects started with good performance (longer for the left hand), a position- and velocity-dependent curl force field that perturbed the trajectories was introduced. The force F applied to the fingertip was defined as $F = C(k_p p + k_v v)$, where C is a 2×2 90° rotation matrix (curl) in the principal plane of the fingertip movement (H), p and v are the position (from the center) and velocity vectors projected into the principal plane of fingertip movement (Figure 1B), and $k_p = 80 \text{ Nm}^{-1}$ and $k_v = 5 \text{ Nm}^{-1} \text{ s}$. The force field, therefore, had a component that perturbed the finger in

a manner proportional to its current speed and orthogonal to the direction of movement (velocity component) and a force component proportional to the distance from the center and orthogonal to the line connecting the current finger to the center (position component). Selection of this force field maximized difficulty without causing excessive fatigue. An index of the deviation from the straight line computed on the previous movement was graphically displayed at all times so that the subjects were motivated to fully compensate for the external disturbance. After 10 blocks, each block consisting of a movement to each of the six targets, subjects rested for 15 min, during which either rTMS or sham rTMS was applied to their contralateral M1. The task was then immediately resumed for an additional 30 blocks. For each target, a trial without a force field ("catch" trial) was randomly introduced in one of the final six blocks.

Ballistic Movement Experiments

This task was similar to that used by [3]. Subjects were required to abduct their index finger as rapidly as possible. Peak initial acceleration of the previous movement was graphically displayed on screen for motivation. Subjects performed 150 trials before rTMS or sham rTMS and 150 trials afterwards. This choice ensured that in both BM and FF tasks, rTMS was applied when subjects had reached approximately 90% of their asymptotic performance. For purposes of comparison with the FF experiments, six movements were considered as a block.

Transcranial Magnetic Stimulation

In both tasks, the first dorsal interosseus (FDI) activity was monitored via differential EMG. A TMS coil was placed at the site that elicited maximal motor evoked potentials in FDI at 60%–70% stimulator output. TMS was applied during the 15 min period between the learning tasks at 1 Hz and 120% of the motor threshold (MT) via a figure-of-eight coil and a Magstim rapid stimulator (The Magstim Company, Whitland, U.K.). As control, sham rTMS was used rather than ipsilateral rTMS because the latter can produce effects on homologous M1 [25] and premotor regions [26]. For these SHAM experiments, the coil was placed orthogonally to the head.

Data Analysis

In the force field experiments, trajectory straightness was estimated as follows: the root mean square deviation to a line connecting the center to the target was divided by movement extent. In the ballistic-movement experiments, acceleration was obtained by performance of a numerical double differentiation of the position data over a 10 ms time window. For statistical analysis, performance was averaged over four periods of the learning phase: early preTMS (second and third blocks) and late preTMS (last two blocks before rTMS), early postTMS (second and third blocks after rTMS) and late postTMS (last five blocks before the introduction of catch trials). ANOVA (target and period effects) and paired t tests were used for assessing the effect of the rTMS application.

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