

Report

Modification of Existing Human Motor Memories Is Enabled by Primary Cortical Processing during Memory Reactivation

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Summary

One of the most challenging tasks of the brain is to constantly update the internal neural representations of existing memories. Animal studies have used invasive methods such as direct microfusion of protein inhibitors to designated brain areas, in order to study the neural mechanisms underlying modification of already existing memories after their reactivation during recall [1–4]. Because such interventions are not possible in humans, it is not known how these neural processes operate in the human brain. In a series of experiments we show here that when an existing human motor memory is reactivated during recall, modification of the memory is blocked by virtual lesion [5] of the related primary cortical human brain area. The virtual lesion was induced by noninvasive repetitive transcranial magnetic stimulation guided by a frameless stereotactic brain navigation system and each subject's brain image. The results demonstrate that primary cortical processing in the human brain interacting with pre-existing reactivated memory traces is critical for successful modification of the existing related memory. Modulation of reactivated memories by noninvasive cortical stimulation may have important implications for human memory research and have far-reaching clinical applications.

Results

Consolidation has been referred to as resistance of a memory to interference [6, 7] and as memory improvements that take place after the end of the training session (offline gains) [8, 9] involving well-studied neural mechanisms [10–12]. In daily living activities, beyond this initial consolidation period, memories are further modified (reconsolidated) after being reactivated during recall [1–4], showing additional strengthening and offline gains [13]. Because most skills are acquired over time, like learning to play a sport or musical instrument, they engage repetitive reconsolidation processes [13]. To address the question of the neurobiological basis of this process, we chose a memory task in which initial memory formation through consolidation followed by memory modification through reconsolidation have been previously documented [13]. All subjects performed a sequential finger-tapping motor memory task on three separate days [13], with the number of correct sequences performed during each fixed 30 s trial as the primary outcome measure (see Figure 1A and Experimental Procedures) [8, 9]. Consistent with previous

reports, subjects receiving no stimulation showed offline performance gains from day 1 posttraining to day 2 test as a measure of consolidation of the motor memory, followed by additional improvements between day 2 test and day 3 retest pointing to further modification and strengthening of the motor memory through reconsolidation [8, 9, 13] (experiment 1, see Experimental Procedures and Supplemental Information, Figure S1, available online).

Could a transient virtual lesion of the related primary cortical processing node during reactivation of the existing memory block further memory modification? To address this question we conducted a second experiment, in which repetitive transcranial magnetic stimulation (rTMS) guided by a frameless stereotactic brain navigation system and each subject's magnetic resonance imaging (MRI) was applied to the primary motor cortex (M1) during reactivation of the motor memory. Subjects ($n = 10$) performed the task on day 1, and were then tested on day 2 as in the previous experiment (see Figure 1B), showing improved performance (from day 1 posttraining to day 2 test, by mean $20.4\% \pm 4.2\%$ standard error of the mean [SEM], $p < 0.002$) and consolidation of the motor memory (see Figure 1C). There were no significant differences in day 1 posttraining performance ($p = 0.62$), day 2 test ($p = 0.86$), nor in initial consolidation ($p = 0.65$) between the groups in experiments 1 and 2.

After day 2 test, subjects received 15 min of 1 Hz rTMS to M1 (see Figure 1B). During stimulation subjects performed three additional recall trials in order to reactivate the motor memory trace, as required for reconsolidation [1–4]. On day 3 subjects were retested. Results showed that the transient disruption of activity in M1 by rTMS during reactivation of the memory blocked further memory gains from day 2 test to day 3 retest ($p = 0.35$, Figure 1C). These nonsignificant differences in performance during memory modification between test and retest were significantly lower than the performance improvements evidenced during consolidation between posttraining and test ($p < 0.03$, Figure 1C). Furthermore, the nonsignificant differences in performance between test and retest when M1 was stimulated were significantly lower than the improvements between test and retest obtained in the first experiment ($p < 0.04$). Therefore, these results show that during reactivation of the motor memory, interference with M1 processing blocks modification of the memory between test and retest.

Next, we wanted to verify the anatomical specificity of the effects of rTMS applied over M1 on modification of the motor memory. In the third experiment, subjects ($n = 11$) underwent the same experimental procedure, only the rTMS was applied to a vertex control position with the same stimulation parameters as in the second experiment (see Figure 2A). Subjects showed improved performance from posttraining to test (by $16.7\% \pm 4.2\%$, $p < 0.002$) and consolidation of the motor memory (see Figure 2B). There was no significant difference in posttraining performance ($p = 0.98$), in day 2 test ($p = 0.64$), nor in initial consolidation ($p = 0.54$) compared to experiment 2. However, subjects continued to improve between test and retest (by $13.5\% \pm 2.6\%$, $p < 0.0003$, Figure 2B), pointing to efficient memory modification. There were no significant differences between initial

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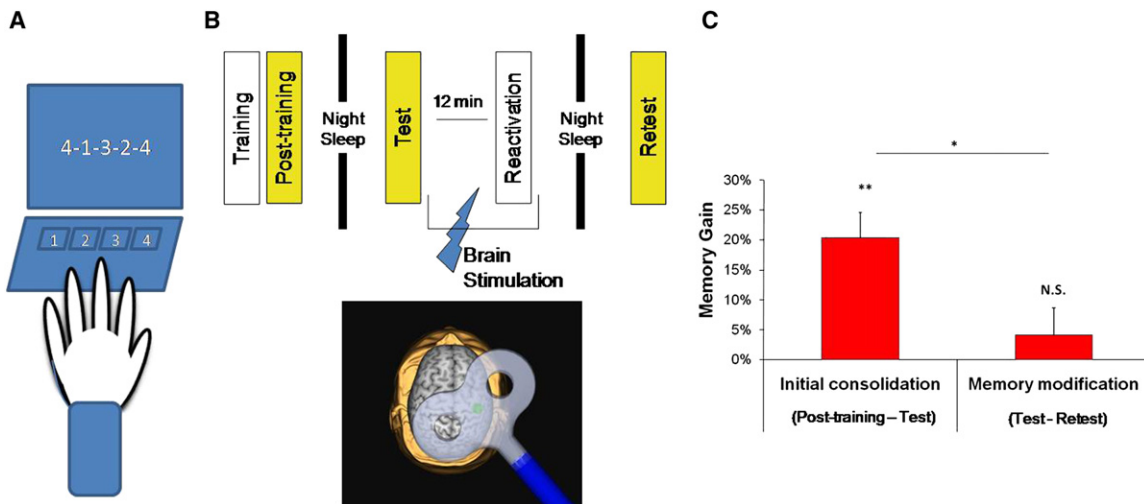


Figure 1. Blocking Memory Modification with rTMS during Memory Reactivation

(A) Subjects performed a sequential finger-tapping task in which they had to repeatedly perform with their nondominant left hand a specific constant sequence of finger movements [9, 13] (see [Experimental Procedures](#)). (B) Subjects were trained on day 1 and then performed posttraining trials. On day 2, subjects were first tested, and then 1 Hz rTMS was applied to M1 for 15 min containing three reactivation trials of the motor memory. The coil was positioned and maintained online via a stereotactic brain navigation system and each subject's MRI. Subjects were retested on the third experimental day. (C) Performance improved from posttraining to test (initial consolidation), similar to controls (see [Figure S1](#)), however stimulation blocked memory gains between test and retest, blocking modification of the memory. There were significant differences between initial consolidation and memory modification gains. Error bars show SEM. Repeated-measures analysis of variance (ANOVA) and paired t tests were used. **, $p < 0.005$; *, $p < 0.05$; N.S. denotes non-significance.

consolidation and memory modification gains ($p = 0.27$, [Figure 2B](#)). These memory modification gains were significantly higher than the nonsignificant memory modification gains observed when M1 was stimulated ($p < 0.05$). These results indicate that the effects of rTMS applied during reactivation of the motor memory were not generalized to stimulation of a control brain region, pointing to the specific role of this primary cortical processing unit in modification of the related memory.

To address the question whether stimulation of M1 blocked memory modification because of disruption of manual performance during reactivation ([Figures 1B and 1C](#)), we applied 1 Hz stimulation to the ulnar nerve at the wrist. Stimulus intensity was that required to induce a disruption of manual performance during reactivation equivalent to that elicited by rTMS (see [Figure 3A](#) and [Experimental Procedures](#)). Subjects ($n = 10$) showed improved performance from posttraining to test (by $22.4\% \pm 3.4\%$, $p < 0.0002$) and consolidation of the motor memory (see [Figure 3B](#)). There was no significant difference in posttraining performance ($p = 0.90$), in day 2

test ($p = 0.90$), nor in initial consolidation ($p = 0.71$) compared to experiment 2. However, subjects showed significant memory gains between test and retest (by $15.9\% \pm 3.2\%$, $p < 0.0003$, [Figure 3B](#)), pointing to efficient modification of the motor memory. There were no significant differences between initial consolidation and memory modification gains ($p = 0.13$, [Figure 3B](#)). These memory modification gains were significantly higher than the nonsignificant memory modification gains observed when M1 was stimulated ($p < 0.03$). These results rule out the possibility that disruption of performance per se during memory reactivation blocked further modification of the memory, indicating that disruption in specific M1 processing during memory reactivation was responsible for blocking memory modification.

Discussion

With the use of noninvasive techniques applicable for experimental human brain research, these findings identify specific cortical mechanisms necessary for existing human memory modification. The results show that during recall of an existing

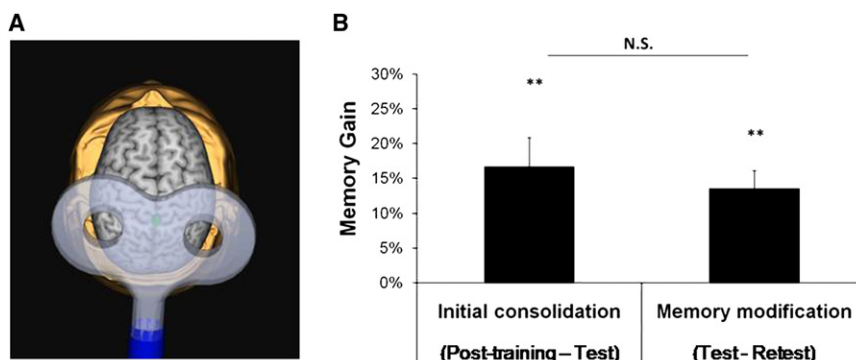


Figure 2. Cortical Specificity

(A) 1 Hz rTMS was applied to the vertex control site immediately after the test trials and during the reactivation trials of the motor memory. (B) Performance improved from posttraining to test similar to previous experiments. However, vertex stimulation, contrary to M1 stimulation, did not affect memory modification. Error bars show SEM. **, $p < 0.005$; *, $p < 0.05$; N.S. denotes non-significance.

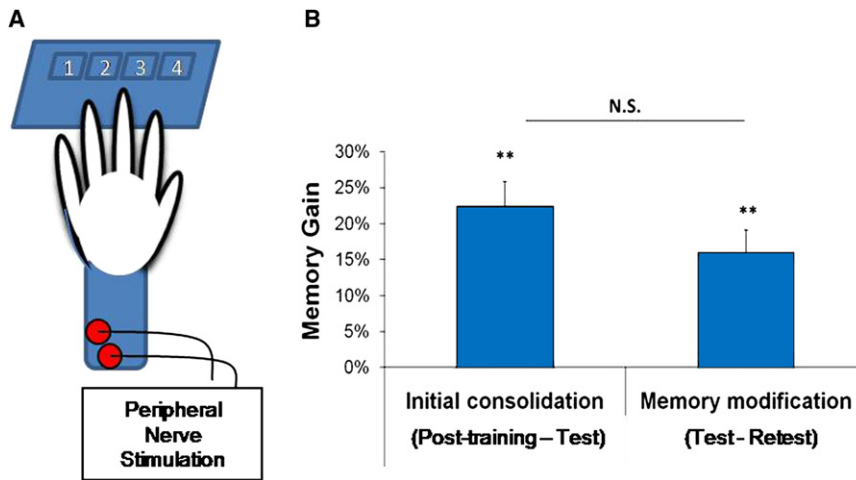


Figure 3. Disruption of Performance Per Se during Memory Reactivation Does Not Block Memory Modification

(A) The ulnar nerve at the wrist was stimulated at 1 Hz during the three reactivation trials at an intensity causing an equivalent disruption of performance during reactivation as when M1 was stimulated (see Experimental Procedures). (B) Stimulation did not affect memory modification, as opposed to when M1 was stimulated. Error bars show SEM. **, $p < 0.005$; *, $p < 0.05$; N.S. denote nonsignificance.

motor memory, that memory becomes susceptible to further modification dependent on specific primary motor cortex processing. Our finding that interference with M1 processing during memory reactivation did not degrade the original memory trace is also consistent with the view that the core storage site of the consolidated memory involves additional brain regions such as the cerebellum, striatum, and/or other motor-related cortical areas [14–16]. It has been previously suggested that reconsolidation could be looked upon as lingering consolidation [2]. Together with previous studies proposing that reconsolidation may represent the basis of strengthening of memories through additional training [2, 3], our results may suggest that recurrent interactions of M1 processing with existing memory traces may be critical for further memory modification through reconsolidation. Previous rTMS studies [10, 11] have shown that rTMS to M1 after task performance did not block overnight offline gains, or, had no interference effects on memory beyond the initial consolidation phase. Together with our results, these data suggest that combination of rTMS with memory reactivation, as carried out in our study, is necessary to modify the existing memory as required for reconsolidation [1–4].

are transformed over time into inactive memory states [4, 17], mediated through differential cellular processes [18]. They proposed that reactivated memories may be modified while being temporarily in their active state. Although such models characterize active memory and inactive memory as functional states, different storage domains or specific human neural substrates involved have not been clearly identified. Based on the results shown here we suggest the following model for human motor memory modification (see Figure 4): Primary cortical human brain areas (such as primary motor cortex in the motor domain) serve as the executing memory storage domain that interacts with the environmental stimuli (passive exposure, active task, or manipulations such as brain stimulation). The output from this executing storage domain updates the core storage domain, enabling memory modification. Upon memory reactivation, recurrent output from the core storage domain to the executing storage domain enables memory modification after interaction with the environment. Direct interactions between the core storage domain and the environment not engaging the executing storage domain remain to be determined, along with associations to suggested dual-layered memory representation models [19].

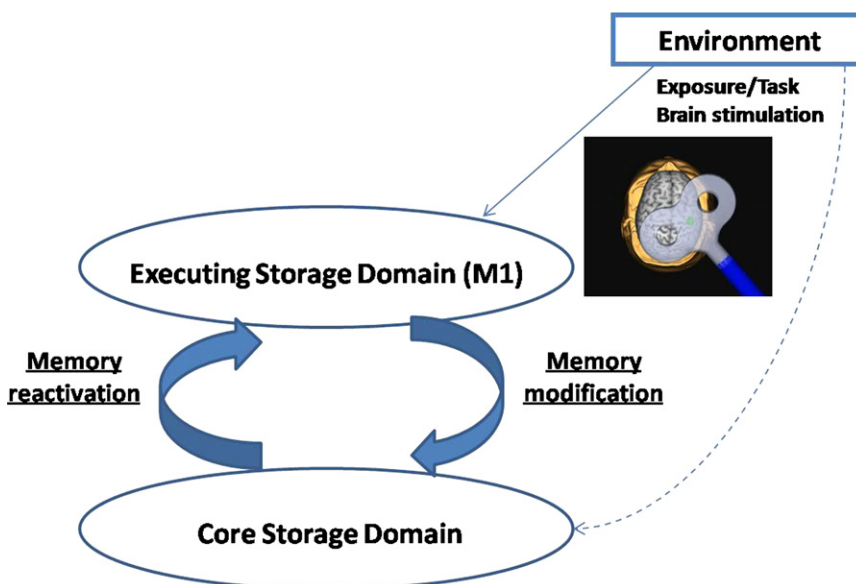


Figure 4. A Model for Human Motor Memory Modification

The model differentiates not only between functional memory states but also between memory storage domains (see text). Upon memory reactivation, recurrent output from the core storage domain to the primary cortical executing domain which interacts with the environment enables further memory modification. Direct interactions between the core storage domain and the environment not engaging the executing storage domain remain to be determined.

Furthermore, it remains to be determined which brain areas may be involved as part of the core storage domain, with previous studies possibly pointing to areas such as the cerebellum, striatum, and/or other motor-related cortical areas [14–16], and areas such as the hippocampus which was shown to have a role in the development of procedural motor memories [20].

Whereas previous memory reconsolidation research focused mainly on animal studies allowing invasive interventions, this study suggests an explanation of how existing memories are modified in the human brain. Such noninvasive interventions allow differentiation not only between functional memory states but also between memory storage domains as suggested by the model. Further experimental work is needed in order to test whether human primary cortical brain areas contribute to memory modification in other sensory modalities. The identification of a mechanism underlying human memory modification may be relevant to the treatment of conditions involving memory deficits by facilitating cortical functions [21–23]. Thus, better understanding of such memory dynamics over time may be important for development of rational interventions to improve memory gains or to prevent forgetting.

Experimental Procedures

Subjects

Forty-one naive right-handed healthy subjects (19 men, 22 women; age mean 26.9 ± 3.8 standard deviation [SD]) participated in the study. All subjects gave their written informed consent to participate in the study, which was approved by the National Institute of Neurological Disorders and Stroke (NINDS) Institutional Review Board. Participation required a normal neurological examination, reporting at least 6 hr of sleep the night before each experimental session, not being an active musician, and ability to perform the basic motor task with improved performance (offline gains) from day 1 posttraining to day 2 test.

Task

We used the sequential finger-tapping task [8, 9]. Each trial was 30 s, in which subjects had to repeatedly tap with their nondominant left-hand fingers as quickly and accurately as possible a specific sequence of finger movements on the computer keyboard (see Figure 1A) [8, 9]. The same sequence was used in all experiments and sessions. During each trial, the sequence (4-1-3-2-4) appeared on the screen to eliminate any working-memory components. Partial feedback was given, with each key press producing a dot on the screen (rather than the tapped digit itself) and with the dots forming a row from left to right. Each trial was followed by a 30 s break until the next trial started. As in previous studies, the number of correct sequences performed during each fixed 30 s trial was the primary outcome measure [8, 9].

Procedure

In all experiments, subjects performed on day 1 nine training trials followed by three posttraining trials (see Figure 1B). On day 2, all subjects first performed three test trials. Subjects then performed three additional reactivation trials with no stimulation (experiment 1), with rTMS to M1 (experiment 2), with rTMS to the vertex (experiment 3), or with peripheral stimulation of the ulnar nerve (experiment 4). On day 3, subjects in all experiments performed three retest trials. All sessions were performed before 2 p.m. in the afternoon, with subjects instructed to continue their usual daily routine. All subjects reported sleep of at least 6 hr the night before each experimental session.

Stimulation and Neuronavigation

In experiments 2 and 3, 1 Hz rTMS was applied to M1 and the vertex (respectively) immediately after the test trials for 15 min containing three reactivation trials of the motor memory. Stimulation intensity was adjusted for each individual subject, producing 5 out of 10 motor evoked potentials (MEPs) greater than 1 mV as recorded from the left first dorsal interosseous (FDI) muscle. Average stimulus intensity was 119% (SD $\pm 6.5\%$) of rMT

defined as the minimum stimulus intensity required to produce at least 5 out of 10 MEPs greater than 50 μ V [24]. Surface electromyogram (EMG) was recorded from surface electrodes positioned on the skin overlying the FDI muscle (bandpassed 25 Hz to 1 kHz, sampled at 2 Hz). A Magstim standard double coil (loop diameter 70 mm) connected to a rapid-rate magnetic stimulator (Magstim Company, Whitland, UK) was positioned on the scalp over the right M1 or the vertex. The position of the coil was maintained online via a brain navigation system (Brainsight, Rogue Research, Montreal, Canada) and each subject's MRI. In experiment 4, the ulnar nerve was stimulated at 1 Hz during the three reactivation trials at an intensity causing an equivalent disruption of performance during recall as in experiment 2 (with no significant differences in performance between the groups, $p = 0.51$).

Data Analysis

The outcome measure was the number of correct sequences achieved per trial. For each subject, performance was averaged over the posttraining trials and each set of test and retest trials. To exclude effects of fatigue, we excluded the last trial in cases in which there was a sudden drop in that trial of 25% or more in performance and a 3-times-or-more increase in tapping errors performed. Comparisons within each experimental group were performed with repeated-measures analysis of variance (ANOVA) and paired *t* tests with the Bonferroni correction for multiple comparisons. Comparisons between groups were performed with unpaired *t* tests.

Supplemental Information

Supplemental Information includes one figure and can be found with this article online at doi:10.1016/j.cub.2010.07.047.

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