Causal Role of Prefrontal Cortex in Strengthening of Episodic Memories through Reconsolidation

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Summary

Memory consolidation is a dynamic process. Reactivation of consolidated memories triggers reconsolidation, a time-limited period during which memories can be modified [1–4]. Episodic memory refers to our ability to recall specific past events about what happened, including where and when [5]. However, it is unknown whether noninvasive stimulation of the neocortex during reconsolidation might strengthen existing episodic memories in humans. To modify these memories, we applied repetitive transcranial magnetic stimulation (rTMS) [6] over right lateral prefrontal cortex (PFC), a region involved in the reactivation of episodic memories [7, 8]. We report that rTMS of PFC after memory reactivation strengthened verbal episodic memories, an effect documented by improved recall 24 hr postreactivation compared to stimulation of PFC without reactivation and vertex (control site) after reactivation. In contrast, there was no effect of stimulation 1 hr postreactivation (control experiment), showing that memory strengthening is time dependent, consistent with the reconsolidation theory. Thus, we demonstrated that right lateral PFC plays a causal role in strengthening of episodic memories through reconsolidation in humans. Reconsolidation may serve as an opportunity to modify existing memories with noninvasive stimulation of a critical brain region, an issue of fundamental importance for memory research and clinical applications.

Results and Discussion

Consolidation theory assumes that memories are unstable (i.e., susceptible to interference) for a limited time after encoding, but as time passes, memories stabilize and become resistant to interference [9]. Newly formed memories require gene expression for several hours in order to become stable or consolidated [3]. However, studies done in the last decade demonstrated that the initial gene-expression-dependent phase is not the only one [1–3]. In fact, consolidated memories can re-enter unstable states when they are reactivated during retrieval or by a reminder cue and need to consolidate again in order to persist over longer periods of time [1–4]. Thus, the concept of reconsolidation assumes that memories are not consolidated once and forever, challenging the view that stability characterizes consolidated memories [2–4]. Indeed, memory reactivation triggers reconsolidation, a time-limited period during which existing memories are susceptible to modifications [1–4]. Thus, memories can be stabilized, strengthened [10–13], weakened/disrupted [1, 14, 15], or updated by the inclusion of new information [16, 17] through reconsolidation.

Episodic memory refers to our ability to recall specific details about past events, including where, when, and what happened [5]. The prefrontal cortex (PFC) is a critical node in the neural network mediating the encoding and retrieval of these memories [7, 16].

Although previous human studies on reconsolidation have shown that existing episodic memories can be enhanced by stressor events [16], emotional processing [11], successive reactivations of the memories [12], or pharmacological modulations [13], it remains unknown whether the lateral PFC plays a causal role in the reconsolidation process.

To modify episodic memories, we applied repetitive transcranial magnetic stimulation (rTMS) over right lateral PFC. Since retrieval or reactivation by a reminder cue triggers reconsolidation, we decided to stimulate a neocortical region involved in retrieval [7, 18] and reactivation of episodic memories [6]. Previous rTMS studies demonstrated the causal role of right, but not left, lateral PFC in retrieval [7, 18], and these findings were confirmed in a functional resonance magnetic imaging (fMRI) study showing activation of the right, but not left, lateral PFC during memory reactivation by a reminder cue [8]. rTMS is a noninvasive brain stimulation technique used in this protocol to evaluate the causal role of focal neocortical regions and to modulate cognitive function [6, 19] (see the Supplemental Experimental Procedures available online).

Subjects (n = 30) learned a list of 20 object words on day 1. This procedure was repeated until the participants remembered at least 17 of the 20 words (85%) or until a maximum of four learning trials was reached [16, 17]. On day 2, in a subset of subjects (n = 10), existing memories were reactivated by a spatial-contextual reminder cue (without explicit recall), and 10 min later 1 Hz rTMS was applied for 15 min to right dorsolateral PFC (PFC-R) (see the Supplemental Experimental Procedures). There is evidence that memories are automatically reactivated if the original learning spatial context is part of the reminder [17]. To determine whether the rTMS effect was specific to memory reactivation and relied on right PFC function, we designed two control conditions that were applied to the remaining subjects (n = 10 per group). First, to determine whether the rTMS effect was specific to memory reactivation, we applied rTMS over right PFC without memory reactivation (PFC-NR), a behavioral manipulation previously successfully done in animal [1] and human [16] reconsolidation studies. Second, to determine whether the rTMS effect was topographically specific, we applied rTMS over the vertex after memory reactivation (vertex-R, control site) [6]. We chose the frequency of rTMS on the basis of a recent study showing that 1 Hz rTMS of right lateral PFC enhanced episodic memory performance when delivered during the interval (10 min) between encoding and retrieval [20]. Memory recall was tested on Day 3 (24 hr postreactivation) (see Figure 1 and the Supplemental Experimental Procedures).

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In order to compare the learning rate of the three experimental groups, we recorded how many learning trials (1–4) were necessary for participants to recall at least 17 words (85%) on day 1. Participants needed on average 3.4 learning trials to reach this criterion (PFC-R = 3.3 ± 0.26 [mean ± SEM]; PFC-NR = 3.5 ± 0.22; vertex-R = 3.4 ± 0.27). There were no significant differences between the three groups (H = 0.133, p = 0.93).

Regarding the number of words recalled on day 3 (see the Supplemental Experimental Procedures), the main effect “group” was significant [F(2,27) = 6.30, p < 0.01]. Independent t tests (Bonferroni corrected, p = 0.0167) showed significant differences between PFC-R (14.3 ± 0.63) and PFC-NR (11.3 ± 1.05) (p < 0.0161) and between PFC-R and vertex-R (11.3 ± 0.45) (p = 0.0006). No difference was found between PFC-NR and vertex-R (p = 0.9658). To enable comparison between experiments, we have displayed the mean percentage of words recalled in each group in Figure 1 (PFC-R = 73% ± 3.17%; PFC-NR = 56.3% ± 5.24%; vertex-R = 56.6% ± 2.27%).

These findings show that stimulation of right PFC after memory reactivation (PFC-R) strengthened verbal episodic memories, an effect indicated by enhanced later recall (24 hr postreactivation) compared to rTMS of PFC without memory reactivation (PFC-NR) or rTMS of a control site after memory reactivation (vertex-R).

To determine whether the rTMS effect (PFC-R) was reconsolidation specific, we carried out a control experiment (experiment 2). Because reconsolidation is a process requiring gene expression for several hours [2, 3], memory modification should not be expressed shortly postreactivation (i.e., 1 hr, when the memories are still unstable) but many hours later (i.e., 24 hr, after memories have become stable again) [2, 3, 13, 16]. In animal studies, memory reconsolidation is only observed after a delay of about 4 hr [2].

To address this question, in experiment 2 we used exactly the same materials and followed exactly the same procedure as in experiment 1 with one exception: the experiment consisted of only two experimental sessions in consecutive days (24 hr apart). The procedure described for day 3 in experiment 1 (i.e., memory recall) was administered on day 2 shortly (i.e., 30 min) after the end of the rTMS session (1 hr postreactivation). This 30 min interval was chosen to allow the aftereffects of rTMS to wash out in order to avoid effects on the retrieval process per se [6]. Based on the findings of experiment 1, we compared right PFC-R (n = 10) to vertex-R (n = 10) (see Figure 2).

Subjects (n = 20) needed on average three learning trials to recall at least 17 words (85%) (PFC-R = 3 ± 0.30; vertex-R = 3 ± 0.26). No significant differences were found between the groups (U = 48.0, p = 0.87).

Regarding the number of words recalled on day 2 (see the Supplemental Experimental Procedures), the main effect of “group” [F(1,18) = 0.133, p = 0.72; PFC = 13.85 ± 0.95; vertex = 13.4 ± 0.95] was not significant. The mean percentage of words recalled in each group is displayed in Figure 2 (vertex-R = 67% ± 3.94%; PFC-R = 69.25% ± 4.74%).

Figure 2 shows that, in opposition to findings with recall on day 3 (24 hr postreactivation), testing shortly (1 hr) postreactivation on day 2 yielded comparable results for both vertex-R and PFC-R stimulation. These results suggest that the effect of experiment 1 is time dependent because it is only seen if the memory trace is allowed to reconsolidate.

In this study, we show that rTMS of right lateral PFC after memory reactivation (PFC-R) strengthens existing verbal episodic memories in humans, an effect indicated by enhanced later recall (24 hr postreactivation) compared to control groups (i.e., vertex-R and PFC-NR). Moreover, this effect does not occur when memory performance was tested shortly postreactivation (1 hr). Thus, as predicted by reconsolidation theory [2, 3], the effect of rTMS over right lateral PFC evolves over time and depends on memory reconsolidation.

In this study, we demonstrate for the first time that reconsolidation may serve as an opportunity to strengthen existing
Prefrontal Cortex and Memory Reconsolidation

episodic memories with non-invasive stimulation of the right lateral PFC, showing that enhanced recollection can be achieved by targeting a critical brain region during a postreactivation state of plasticity.

Regarding the putative brain mechanisms of this effect, the role played by spatial context in memory reactivation [17] points to hippocampal involvement in this paradigm [4] and suggests possible functional interactions between this brain region and PFC during the reconsolidation process [21]. It is well recognized that memory consolidation involves a relatively brief cascade of molecular and cellular events that alter synaptic efficacy as well as a prolonged systems level interaction between the hippocampus and neocortex [4, 21]. Episodic memories initially consist of two components: content representations dependent on neocortical networks and a spatial-contextual representation dependent on the hippocampus [4], which seems to serve as the memory trace that permits the retrieval of memory content stored elsewhere [22].

Since rTMS affects not only the targeted local region but also activity in remote interconnected regions [6, 19], 1 Hz rTMS of right PFC after memory reactivation may have enhanced the functional coupling between the PFC and the hippocampus, thereby enhancing memory recollection through reconsolidation. There is evidence that 1 Hz rTMS may improve performance of a cognitive task by strengthening the connectivity between task-relevant brain regions depending on the functional state of the cortex at the time of stimulation [23]. Thus, combined TMS-fMRI studies may shed light on how functional interactions between remote but interconnected brain regions may support reconsolidation of episodic memories [6, 19]. Future work might identify the time window of memory reconsolidation by varying the interval between memory reactivation and rTMS and address the question of whether the same or different lateral PFC regions (i.e., left versus right and dorsal versus ventral) operate in both consolidation and reconsolidation.

We conclude that right lateral PFC plays a critical role in the neural network that mediates the strengthening of episodic memories through reconsolidation in humans.

Noninvasive stimulation of a critical brain region during reconsolidation may be a new opportunity for designing well-controlled, double-blinded interventional studies, which can potentially strengthen adaptive memories in elderly adults and individuals with memory dysfunctions (e.g., mild cognitive impairment) or disrupt maladaptive memories in individuals with posttraumatic stress disorder.

Experimental Procedures

The experimental procedures are summarized briefly throughout the Results and are presented in complete detail in the Supplemental Experimental Procedures.

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.08.045.

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