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Modulating reconsolidation: a link to causal systems-level dynamics of human memories

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A vital property of the brain is its plasticity, which manifests as changes in behavioral performance. Invasive studies at the cellular level in animal models reveal time-restricted windows during which existing memories that are reactivated become susceptible to modification through reconsolidation, and evidence suggests similar effects in humans. In this review we summarize recent work utilizing noninvasive brain stimulation in humans to uncover the systems-level mechanisms underlying memory reconsolidation. This novel understanding of memory dynamics may have far-reaching clinical implications, including the potential to modulate reconsolidation in patients with memory disorders.

Memory consolidation and modification through reconsolidation

Memory plays a crucial role in everyday life. It encompasses one's ability to recall an event that occurred in the past, retrieve knowledge that is stored in the brain, and execute motor skills that one has learned. From a cognitive perspective, memories are acquired (encoding), stored, maintained, and later retrieved (retrieval). The process that transforms the acquired information into long-term memory (LTM) is known as memory consolidation (see Glossary). The consolidation model assumes that memories are labile and unstable (i.e., susceptible to interference) for a limited time after encoding, but that as time passes, memories stabilize and become resistant to interference [1].

Two levels of description and analysis are used to describe the consolidation process. Synaptic consolidation involves the activation of intracellular signaling cascades, modulation of gene expression, and synthesis of gene products that alter synaptic efficacy. This form of consolidation is completed within hours from its initiation [2]. Systems-level consolidation refers to the reorganization of LTM over distributed brain networks. This process may last from days to years, depending on the memory system [2]. In addition, sleep optimizes the consolidation of some types of newly encoded information in memory [3].

It is now widely accepted that memories are dynamic, even after their initial stabilization through consolidation. Accumulating evidence has shown that consolidated

Glossary

Consolidation: the processes that stabilize memories after encoding, transforming them into long-term memory (LTM).
Electroconvulsive therapy (ECT) or electroconvulsive shock: the application of a short-acting anesthesia followed by electrical stimulation to the cranium, evoking generalized seizure activity. The mechanism of action by which ECT affects memory and may disrupt reconsolidation remains largely unknown [5,49].
Episodic memory: a type of declarative memory that refers to the conscious recollection of events [84]. It is mediated primarily by the prefrontal cortex (PFC) [27,78,85] and medial temporal lobe [85], particularly the hippocampus. Variations in the strength of links between hippocampus and neocortex are at the heart of different studies in the field of memory consolidation [2]. The standard model of systems-level consolidation posits that encoding, storage, and retrieval of information is initially dependent on the hippocampus as well as on neocortical areas relevant to the encoded stimuli. Over time, this information reorganizes and becomes integrated in the neocortex and independent of the hippocampus [2]. An alternative model, the multiple-trace theory, posits that the links between hippocampal and cortical representations remain crucial, and thus the hippocampus is continuously involved in the storage and retrieval of memories [2].
Extinction training: manipulation in which the fear memory is diminished by repeated presentations of the conditioned stimulus without the aversive outcome.
Functional connectivity: correlation between remote neurophysiological events in the temporal domain [86].
Nondeclarative memory: refers to processes in which learning has occurred, which is reflected in performance rather than through overt remembering (e.g., fear memories, procedural motor skills) [84]. Although memories created by aversive or rewarding reinforcement rely primarily on the PFC [25,61,87] and the amygdala [60,61,88], memories of motor skills rely on activity in a distributed network that includes the motor cortex, striatum, and cerebellum [74].
Prediction error: a discrepancy between actual and expected events. It can be influenced by previous learning, reinforcement, or sensory information, and their relation to the actual subsequent events [16–19].
Protein synthesis inhibitors: infused following memory encoding or reactivation to inhibit protein synthesis required for consolidation and reconsolidation, thereby identifying the regional processes involved and linking them with the behavioral expression of memory function [89].
Reconsolidation: the processes that re-stabilize the consolidated memories after reactivation.
Vertex: the scalp midline location referring to the highest point of the skull. Commonly considered as a neutral stimulation site used to control for topographic specificity of the transcranial magnetic stimulation (TMS)-induced effects [70].

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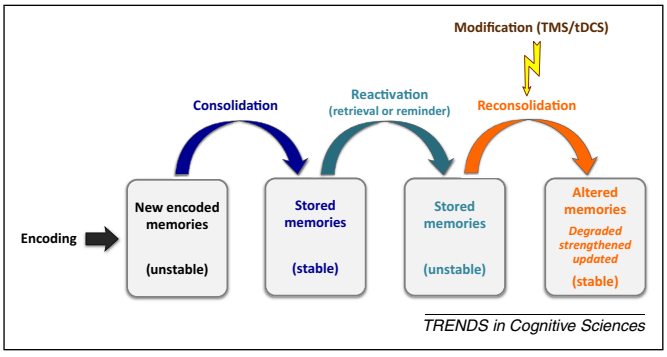

Figure 1. Schematic illustration of memory formation and modification through reconsolidation. Shortly after encoding, new memories are in an unstable/labile state until they are consolidated. Memory reactivation returns the consolidated memories from a stable state to an unstable state again, from which they need to be reconsolidated. During reconsolidation, noninvasive brain stimulation techniques (i.e., TMS, tDCS) can modify the unstable memories, revealing the systems-level mechanisms underlying memory reconsolidation. Thus, existing memories can be degraded, strengthened, or updated by the inclusion of new information through reconsolidation. Modified from [9] with permission from Elsevier.

memories can re-enter unstable states when they are reactivated during retrieval (i.e., the process of recalling or recognizing previous stored information) or by a reminder cue (i.e., external information that is associated with the stored information). These memories must then be consolidated again, or reconsolidated, to persist over longer periods of time [4,5]. Thus, reconsolidation refers to the processes that re-stabilize the consolidated memories after reactivation [6–9]. During the time-limited reconsolidation window, existing memories are vulnerable to modifications. There is evidence that memories can be strengthened, weakened or updated by the inclusion of new information through reconsolidation (Figure 1) [6–9]. However, reconsolidation does not occur every time the existing memory is reactivated. Different boundary conditions have been identified so far, such as the age of the memory [10,11], the strength of training [10,12,13], the reactivation length [10,13–15], and the requirement of novel information at the time of the reactivation session (prediction error) [16–19].

In this review we refer to reconsolidation as the process that allows modification of memory strength or mediates updating of memory content by allowing the integration of new information into the original memory.

Most work on reconsolidation has been performed in animal models because this permits the use of invasive methods such as the infusion of protein synthesis inhibitors into designated brain areas to interfere with neural processes underlying memory (e.g., [4]). However, noninvasive brain stimulation (NIBS) [20] has recently provided a powerful approach for studying brain function in humans. Indeed, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) [20] have been used in the past few years to reveal the mechanisms underlying consolidation and reconsolidation of human memories.

Combining NIBS with neuroimaging [21] through interdisciplinary efforts has also yielded novel insights into human reconsolidation mechanisms at the brain network systems-level [22,23]. This work, for example, demonstrates that modification of previously consolidated human motor skill memories is possible, and shows that processing in primary motor cortex (M1) during memory reactivation is essential for efficient reconsolidation of the memory [24]. In addition, correlated coactivations of M1 and dorsal striatum are altered following interference with a consolidated motor memory, revealing a network in which both regional activity and inter-regional functional connectivity are involved in the reactivation–reconsolidation process [22,23].

In addition to discussing reconsolidation of human motor skill memories, we describe studies that used NIBS to modulate prefrontal cortex (PFC) function [25–27], and demonstrate its causal role in the reconsolidation of episodic memories [27]. We also discuss clinical implications, outstanding questions, and future research directions of such work. Overall, this article will illustrate how NIBS studies complement crucial findings on reconsolidation at the regional cellular level.

Insights from animal models

Extensive studies have been performed in animal models (mainly rodents) to investigate memory reconsolidation. The classical interventions used to modify memory strength through reconsolidation were electroconvulsive shocks [5] and the administration of amnesic agents such as protein synthesis inhibitors [4]. For instance, in a study using the auditory fear-conditioning paradigm [4], a neutral stimulus (conditioned stimulus; i.e., a tone) was paired with an aversive outcome (unconditioned stimulus; i.e., a footshock). After the memory was consolidated, the protein synthesis inhibitor anisomycin was infused into the lateral basal nucleus of the amygdala shortly after the memory for fear was reactivated by the presentation of the tone alone. In the control group, a vehicle (i.e., inactive variant of the drug) infusion was administered after the reactivation of the fear memory. Memory for fear was tested 24 h later by presenting only the tone. Immobility of the animal (freezing) was used as a measure of the retention of the fear response. The results showed that memory for fear was disrupted in the experimental group, whereas in the control group fear conditioning was still present – as well as in another control group in which the drug was infused without memory reactivation (no tone) – suggesting that indeed the reactivation rendered the fear memory unstable again. Moreover, if the drug was infused 6 h after memory reactivation, there was no effect on memory tested the following day, suggesting a limited time-window during which the memory is unstable following its reactivation [4].

The hippocampus has also been shown to be involved in reconsolidation mechanisms [11,17,28,29]. For example, intra-hippocampal infusions of the protein synthesis inhibitor anisomycin blocked hippocampus-dependent contextual fear memory, but only if the memory was reactivated before infusion [29].

Existing memories can be not only weakened but also strengthened through reconsolidation. Some studies have shown memory enhancement during reconsolidation by using different pharmacological agents or modulators that affect the re-stabilization phase [30,31]. Other studies have addressed the strengthening function of reconsolidation by