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Review

Reconsolidation and psychopathology: Moving towards reconsolidation-based treatments

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ABSTRACT

Interfering with memory reconsolidation has valuable potential to be used as a treatment for maladaptive memories and psychiatric disorders. Numerous studies suggest that reconsolidation-based therapies may benefit psychiatric populations, but much remains unanswered. After reviewing the literature in clinical and healthy human populations, we discuss some of the major limitations to reconsolidation studies and clinical application. Finally, we provide recommendations for developing improved reconsolidation-based treatments, namely exploiting known boundary conditions and focusing on a novel unconditioned stimulus-retrieval paradigm.

Contents

Abbreviations: CS, conditioned stimulus; ECT, electroconvulsive therapy; mTOR, mammalian target of rapamycin; NMDA, N-methyl-d-aspartate; PTSD, post-traumatic stress disorder; TMS, transcranial magnetic stimulation; US, unconditioned stimulus.

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1. Introduction

The traditional theory of memory consolidation holds that memories undergo one single consolidation process, a process that converts a short-term memory into a long-term memory (McGaugh, 1966). Once this conversion occurs, the memories are thought to be permanent and resistant to change. However, the conventional theory has recently been displaced by a new theory, one that hypothesizes that whenever memories are reactivated they enter a period of lability, during which time the memories can be altered or updated (Fig. 1A). Notably, certain aspects of the memory (e.g., declarative or emotional components) may have the potential to be independently altered or updated. Following memory destabilization, memories must undergo another round of a consolidation-like process, which has been termed reconsolidation. If the reconsolidation process is interfered with, the memory may be permanently weakened or disrupted, a state that is also known as "amnesic deconsolidation" (Hong et al., 2011).

Memory reconsolidation was first explored in the 1960s, examining the effects of post-retrieval electroconvulsive shock on subsequent amnesia for a fear conditioning memory (Misanin, Miller, & Lewis, 1968; Schneider & Sherman, 1968). Such findings called the consolidation theory into question (Lewis, 1969), but interest in the so-called electroconvulsive shock-induced retrograde amnesia phenomenon soon died out. However, interest in reconsolidation was rekindled around the turn of the millennium (Nader, Schafe, & LeDoux, 2000; Przybyslawski, Roullet, & Sara, 1999; Przybyslawski & Sara, 1997). In the past decade and a half, a plethora of research has since been carried out, and reconsolidation has become an intriguing topic with many proposed therapeutic effects for patients with psychiatric disorders, including post-traumatic stress disorder (PTSD) and addiction (see for recent review, Taylor & Torregrossa, 2015).

In this review article, the clinical treatment potential of reconsolidation-based manipulations will be examined. First, behavioral procedures employed in human studies of reconsolidation will be introduced. Then, the literature on reconsolidation manipulations in clinical populations and in healthy individuals will be discussed. Next, some of the major limitations to reconsolidation studies and clinical application will be overviewed. Finally, we will provide recommendations for developing improved reconsolidation-based treatments, namely exploiting known boundary conditions and focusing on a novel unconditioned stimulus (US)-retrieval paradigm.

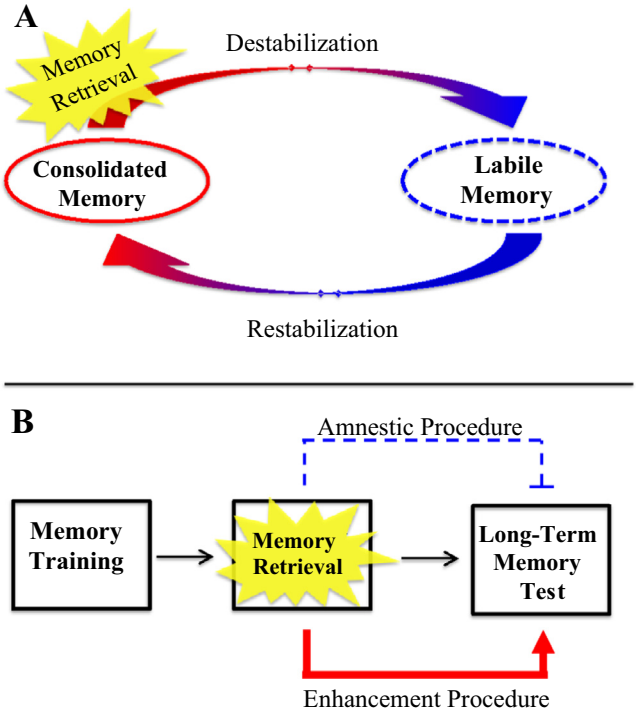

Fig. 1. Memory Reconsolidation Process. (A) A schematic representation of memory reconsolidation. Upon memory retrieval, a consolidated memory destabilizes into a labile memory. The labile memory then restabilizes back into a consolidated memory. (B) A schematic representation of paradigms used to study memory reconsolidation. Following memory training, participants are undergo an amnestic or enhancement procedure (e.g., behavioral procedure or administration of a pharmacological compound) before or after a memory retrieval session. Amnestic and enhancement procedures should decrease or increase memory retention, respectively, on a long-term memory test due to modulation of reconsolidation.

2. Reconsolidation paradigms

Most paradigms used for experimentally studying reconsolidation follow the same basic structure (Fig. 1B). First, participants undergo a training session, during which a new memory is learned. After the memory is consolidated, participants undergo a memory reactivation session in which the memory is briefly reactivated through presentation of either a memory-related cue, in order to induce memory destabilization and lability. Before or after memory reactivation, a pharmacological agent (e.g., propranolol), behavioral procedure (e.g., stress), or non-invasive technique (e.g., transcranial magnetic stimulation; TMS) is administered to enhance or to interfere with reconsolidation. Finally, after the reconsolidation process has ended, a long-term memory test is performed, during which time memory retention is assessed.

Important controls should be included to verify that any effects of the manipulation on long-term memory are due to modulation of reconsolidation. No-reactivation control groups should receive the experimental and control manipulations in the absence of memory reactivation. Memory reconsolidation depends upon post-reactivation memory labilization, and, therefore, the experimental manipulation in the absence of memory retrieval should have no effect on long-term memory. Another control option is a delayed-treatment group, in which memory reactivation takes place but pharmacological or other treatment is administered after the memory has putatively restabilized and is no longer labile. Administration of the experimental manipulation outside of the post-reactivation window of lability should have no effect on long-term memory. In addition to the no-reactivation or delayed-treatment control groups, a short-term memory test can also be administered soon after memory reactivation, before the reconsolidation process has completed. Memory retention should be present in the short-term memory test but not the long-term memory test if the manipulation is interfering with the reconsolidation process. In addition, the inhibition of the memory should be