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Prevention of recurrent affective episodes using extinction training in the reconsolidation window: A testable psychotherapeutic strategy

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ABSTRACT

Stressors may initially precipitate affective episodes, but with sufficient numbers of recurrences, episodes can occur more autonomously. It is postulated the memory engram for these recurrent depressions moves from the conscious representational memory system to the unconscious habit memory system encoded in the striatum. If this were the case, cognitive behavior therapy targeted toward extinction of habit memories could be an effective maneuver for helping reverse the automaticity of affective episode recurrence. Extinction training in the reconsolidation window (which opens about 5 min to 1 h after active memory recall) can revise, reverse, or eliminate the long term memories associated with PTSD and other anxiety disorders and with drug abuse craving. We hypothesize that similar cognitive behavioral work in the reconsolidation window could inhibit stress-induced and spontaneous affective episodes. Some initial formulations of possible therapeutic strategies are presented and discussed, as well as caveats. It is hoped that preliminary exposition of this theoretical approach to recurrences in the affective disorders based on principles dependent on work in the reconsolidation window will lead to more detailed elaboration of the therapeutic maneuvers most likely to be successful and ones that can be specifically tested for their clinical efficacy.

1. Introduction

1.1. Background on memory formation, consolidation, and reconsolidation

Memory formation goes through successive stages of encoding. Hippocampally-based short term memory has long been known to require consolidation into long term memory in the cerebral cortex by a process that requires gene expression and new protein synthesis. In 2000, Nader et al. (2000, 2013) discovered a new later phase in memory storage called reconsolidation. Reconsolidation occurs after a long term memory is actively recalled and the old memory is reprocessed in such a way that it again requires new protein synthesis (Fig. 1). In addition to memory recall, there must be novel information or context for opening of the reconsolidation window (Agren, 2014; Ecker, 2015). Fig. 2.

During this phase of reconsolidation, the memory trace becomes labile and subject to long term revision by psychological processes occurring within the reconsolidation window which lasts approximately 5 min to 1 h (and possibly up to 5 h) after the active memory recall. The original memory trace can either be further strengthened with each new reconsolidation experience or modified and revised if the circumstances and requirements for new learning are met. Ecker (2015) describes "reconsolidation as having two biological functions: (a) It preferentially strengthens recent learnings that are most frequently reactivated and destabilized, and (b) it allows new learning experiences to update (strengthen, weaken, modify, or nullify) an existing learning."

In this manuscript we review some of the pertinent clinical and preclinical data on the use of new learning within the reconsolidation window to alter conditioned fear and memories of positive drug experiences that drive addiction. How these concepts might then be utilized in psychotherapy to attempt to prevent the recurrences of depression are preliminarily outlined, and how these effects could be potentiated by medications is discussed. The potential for exacerbation as well as positively modifying emotional learning is also described. Thus, it is hoped that the current exposition of the role of reconsolidation memory in the psychotherapeutic process will provide further background information for clinicians and investigators wanting to utilize these concepts in the development of more systematic approaches to preventing depressive episodes in the recurrent mood disorders.

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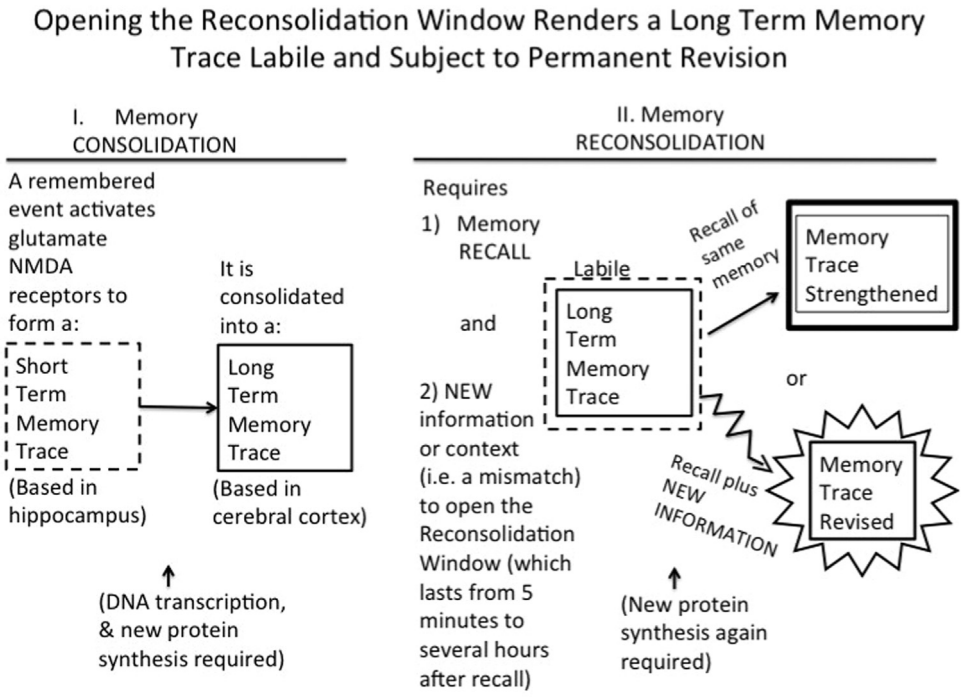

Fig. 1. There are two phases of memory consolidation. Short term memory requires new protein synthesis for I. CONSOLIDATION into long term memory. Active recall of the long term memory in the presence of new information (what has been called mismatch prediction error) activates a phase of II. RECONSOLIDATION, which renders the old memory amenable to revision during a window of about 5 min to several hours after recall. It again requires new protein synthesis. In the RECONSOLIDATION phase the memory can either remain intact and be strengthened (if there is no mis-match) or revised in the presence of new information.

1.2. Conditioned fear: erasure in the reconsolidation window

The memory trace of a conditioned fear association in humans (Agren et al., 2012) can essentially be erased if extinction training occurs in the reconsolidation window, but not at 6 h after recall (by which time the reconsolidation window has closed). In the study of Agren et al. (2012), the appearance of a specific photograph (the conditioned stimulus, cs) that was repeatedly associated with a mild shock (the unconditioned stimulus, ucs) acquired conditioned stimulus properties and the picture itself came to evoke a fear response. Sight of the picture was also associated with activation of the amygdala as seen on functional magnetic resonance imaging (fMRI) and with changes in skin conductance even when no shock is given.

However, after active recall of the memory linking the picture with the shock, the conditioned fear memory trace could be revised by extinction training within the re-consolidation window, ie the repeated

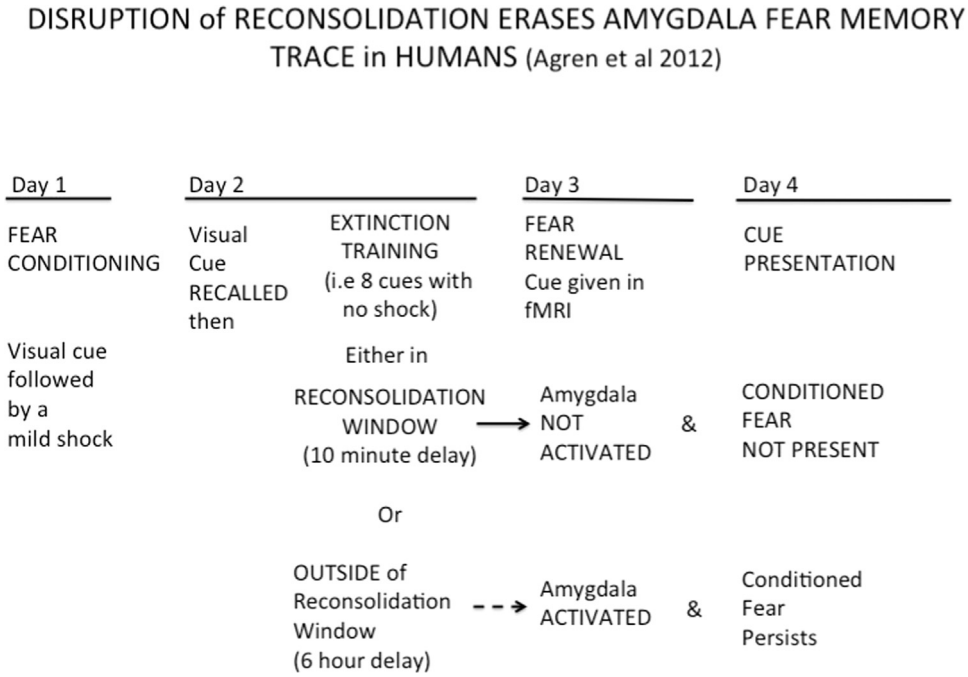

Fig. 2. This study of Agren et al. (2012) shows that in normal volunteers extinction training within the reconsolidation window (the 10 min group) reduces conditioned fear and eliminates the associated amygdala activation seen on the fMRI. These positive results do not occur if the same extinction training is conducted outside of the re-consolidation window (the 6 h delay group).