TOPIC CATEGORY: Memory

TITLE: To Catch A Memory Through Covert Ops

ABSTRACT

Disrupting reconsolidation of the maladaptive memories underlying PTSD could be transformative for treatment. However, patients cannot undergo the direct re-exposure to trauma-cues used to induce reconsolidation in animal studies. Ressler and colleagues report 'covert' memory reactivation in rats, bolstering hopes for translation of reconsolidation-based interventions.

MAIN BODY

Mental health disorders are a major global health problem, estimated to affect 792 million people worldwide[1]. One particularly distressing and debilitating mental health disorder, predicted to increase in prevalence following the global COVID-19 pandemic[2], is post-traumatic stress disorder (PTSD)[3]. PTSD is diagnosed following exposure to a traumatic event (for example, a near-death experience in an intensive care unit) and is characterised by intrusive thoughts of the trauma, flashbacks, nightmares, hyperreactivity and extreme psychological distress to trauma-related cues. A major theory of PTSD suggests that the persistence and pervasiveness of the disorder is due to the formation of maladaptive fear memories that come to dominate cognition and behaviour[4]. Reducing the impact of these maladaptive memories has been a major treatment focus, leading to the development of therapies such as prolonged exposure therapy. However, prolonged exposure is based upon the psychological process of extinction and, despite innovative adaptations to the treatment protocol[5], the maladaptive fear memory still returns in approximately half of patients[6]. Further treatment innovation is clearly needed.

One potential new approach to treating PTSD is to try to disrupt the original fear memory itself. This could be through targeting the initial consolidation of the memory, but for a variety of reasons — including the practical difficulties of reaching those affected by trauma within the 4–6-hour

consolidation 'window' — many investigators have instead focused on targeting fear memory *reconsolidation.* Reconsolidation is the process by which memories can become modifiable under certain conditions of retrieval[7], and although there appear to be specific 'boundary conditions' controlling whether reconsolidation occurs, it has been reported that even old, well-established memories can become susceptible to disruption with amnestic agents following an appropriate 'memory reactivation' session[8]. However, reconsolidation appears to be highly specific to the memories that are reactivated; for example in rats, when two cues are paired with an aversive footshock outcome, reactivation of one cue induces that cue–footshock association to become unstable, but it leaves the non-reactivated cue–footshock outcome intact[9]. This could present a challenge for the translation of reconsolidation-based therapies to the clinic, where reactivation of the memory involves indirect re-exposure (i.e. only some of the cues associated with the trauma are presented), or even imaginal exposure (where the person is asked to imagine the trauma or trauma-related cues). Thus, for reconsolidation purposes the crucial question is: is it possible to cause a memory to become unstable through indirect re-exposure? The data from Ressler and colleagues[10] suggest that it is.

Using a combination of sophisticated behavioural approaches and engram tagging and manipulation techniques in rats, Ressler and colleagues[10] demonstrate that it is possible to 'covertly' reactivate and attenuate a fear memory. To investigate 'covert' reactivation, they used a backwards fear conditioning procedure, which they contrasted to the more usual 'forwards' auditory fear conditioning (**Fig. 1**). In 'forwards' auditory fear conditioning, rats are trained to associate an auditory cue, which acts as a pavlovian conditioned stimulus, with an electric footshock outcome. The cue develops both predictive properties — predicting the delivery of the shock — and affective properties, becoming a fearful stimulus in its own right. Forwards fear conditioning may take place in a specific context, but often rats more strongly associate the cue with shock than the context, because the cue is a better predictor. By contrast, in backwards conditioning, the cue is presented *after* the shock delivery. Consequently, the cue does not predict the shock itself; rather, the context is the better predictor in this situation. However, subsequent presentation of the cue serves to

indirectly reactivate the memory of the context, and thereby (potentially) the context–shock association. This behaviour therefore provides an excellent opportunity for assessing the indirect reactivation of the memory trace, and its neural basis.

Ressler and colleagues[10] first established behaviourally that their hypothesised associative structure was correct, by using extinction of the context to probe subsequent fearful behaviour. While contextual extinction did not affect forwards conditioning (as the cue is the better predictor of shock and overshadows the context), contextual extinction did impair backwards conditioning (where the context is an essential component of the cue→context→shock association). Drawing on the wealth of evidence that implicates the dorsal hippocampus in the representation of contexts, they then compared recruitment of the hippocampus in the two fear-conditioning procedures, finding that backwards conditioning particularly recruited the dentate gyrus. Using a viral-based approach to label the context memory engram with mCherry, they were able to show that subsequent presentation of the cue in a memory-reactivation session led to activation of the same mCherry-labelled engram; molecular evidence supporting the indirect reactivation of the memory trace. Furthermore, when they not only labelled with mCherry, but also tagged the context memory engram with an excitatory DREADD, they found that they were able to produce conditioned freezing with administration of the DREADD agonist clozapine N-oxide (CNO).

Their final experiment explicitly tested the hypothesis that indirect reactivation of the contextual fear memory — through re-exposure to the cue alone — would be sufficient to make the fear memory once again vulnerable to disruption. Specifically, the authors tested whether reconsolidation of the fear memory could be blocked with the protein synthesis inhibitor rapamycin. Consistent with the hypothesis that the 'forwards' fear memory does not recruit or require a contextual memory engram, Ressler and colleagues found that the 'forwards' fear memory remained intact following the administration of rapamycin to the hippocampus in conjunction with cue re-exposure to reactivate the memory. (This is most likely due to the fact that another brain region critical for pavlovian associations, the amygdala, can support the reconsolidation of the cue–fear memory independently of the hippocampus.) By contrast, and importantly, rats that had undergone backwards conditioning

required protein synthesis within the hippocampus for the memory to reconsolidate and persist. When the contextual fear memory was indirectly reactivated through re-exposure to the cue, administration of rapamycin to the hippocampus attenuated subsequent fear. This suggests that it is possible to induce the reconsolidation of memories, even if the target memory is not directly reactivated.

The capacity to indirectly reactivate memories and render them susceptible to disruption overcomes a major potential hurdle in the translation of reconsolidation-based approaches to the clinic, where imaginal-exposure or virtual-reality approaches are far more tractable than direct re-exposure to trauma-related cues. Beyond practical issues — important as they are — this research also has theoretical implications. One major theory of PTSD suggests that trauma memories spread through a memory network, 'contaminating' other memories that were not originally associated with the trauma[11]. Even in 'simple' animal learning procedures like fear conditioning, it is known that a neural circuit supports fearful behaviour, even if research has emphasised the importance of specific structures such as amygdala. Perhaps surprisingly, there has been little research investigating the impact of targeting a memory in one structure within a neural circuit on the representation of the memory in the other components of that circuit. Although Ressler et al[10] did not aim to address this question, it is straightforward to see how the approach they used could allow the impact of both direct and indirect memory reactivation on distributed engrams to be assessed.

Ultimately, as well as providing support for the translation of reconsolidation-based interventions for PTSD, the findings in [10] act as a springboard for a host of future studies. It remains unknown whether older, more remote or more extensively trained memories would also become unstable following indirect reactivation, which would be of great interest and importance considering the evidence supporting systems-level (re)consolidation and known boundary conditions for directly reactivated memories. Related to this, it is possible that other pavlovian memories, such as cue–drug memories that promote relapse in addicted patients trying to remain abstinent, could also be indirectly reactivated; if so, that would extend the impact of the study to other mental health disorders. Beyond pavlovian fear memories, it is not clear whether the instrumental memories that

support action–outcome and habitual behaviour — for example, active or passive avoidance for PTSD — would share the same boundary conditions on reactivation (whether directly or indirectly reactivated). These are important questions that need to be addressed in the field of reconsolidation. What is very clear from the work of Ressler and colleagues[10] is the impact and explanatory power afforded by using sophisticated behavioural approaches alongside cutting-edge neuroscience techniques. Careful and clever design of behavioural procedures is extremely powerful when it comes to understanding the outcome of sophisticated neural manipulations.

BACK MATTER

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FIGURE LEGEND

Figure 1. Backwards conditioning as a method for demonstrating 'covert' capture of a memory. In both forwards (**A**) and backwards (**B**) fear conditioning, rats are trained to associate a conditioned stimulus (CS) with an unconditioned stimulus (US) in a specific context. In forwards conditioning, the CS predicts the delivery of the footshock leading the rat to form a CS→US association (shown in thought bubble). In backwards conditioning, the CS follows the US, causing the rat to form two associations; one of the context→US and another of the CS→context (shown in thought bubble). (**C**) When a rat that has undergone forwards conditioning is presented with the CS, it reactivates the memory of the CS→US association in a manner that is largely independent of the hippocampus. (**D**) When a rat that has undergone backwards conditioning is presented with the CS, it reactivates the memory of the CS→context association, which indirectly reactivates the memory of the context→US association and leads to activation of the hippocampus. (**E**) This indirect memory reactivation procedure can be used to induce destabilisation of the context→US memory, such that it requires protein synthesis to persist in the brain. This can be blocked by rapamycin to attenuate subsequent fear.

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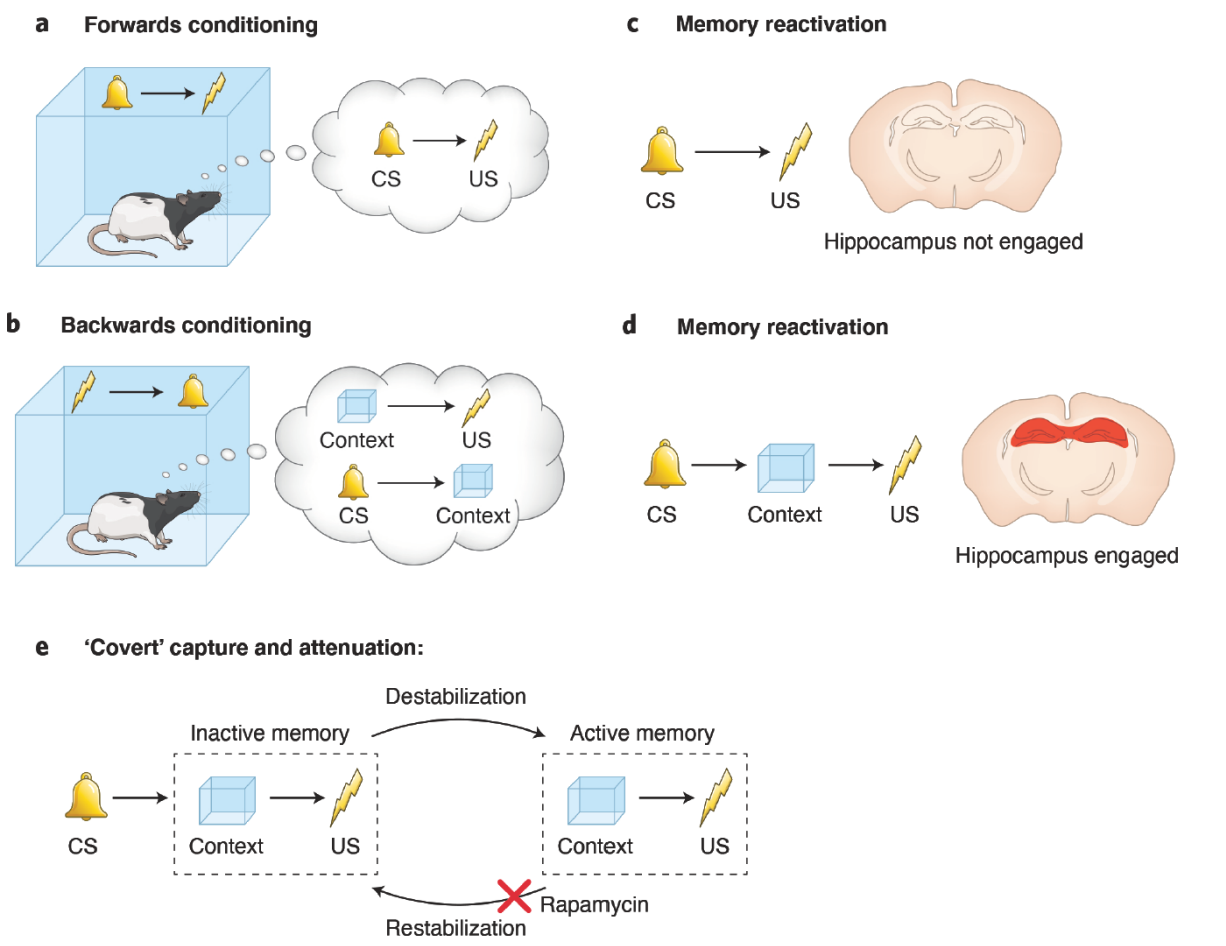
Figure 1


a Forwards conditioning
CS
US
c Memory reactivation
CS
US
Hippocampus not engaged
b Backwards conditioning
Context
US
CS
Context
d Memory reactivation
CS
Context
US
Hippocampus engaged
e 'Covert' capture and attenuation:
Destabilization
Inactive memory
Active memory
CS
Context
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Context
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Rapamycin
Restabilization