Enhancing Cognition by Affecting Memory Reconsolidation

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Abstract (100-120 words)

Fully consolidated associative memories can undergo a retrieval-dependent reconsolidation process, which allows for the updating and strengthening of the original association. Limiting, or so-called boundary, conditions determine whether a particular retrieval event triggers reconsolidation. Manipulating memories at reconsolidation may offer an opportunity to improve cognitive capacities in humans by increasing memory persistence, specificity and accuracy. Also, preventing the reconsolidation of maladaptive memories that characterize some neuropsychiatric disorders, such as post-traumatic stress disorder or drug addiction may offer a novel approach to treatment. Here we review recent advances in understanding and manipulating memory reconsolidation in both animals and humans, and discuss the potential of such interventions in cognitive enhancement.

1. Introduction

Fully consolidated associative memories are stable but not immutable. The presentation of a conditioned stimulus (CS) in the absence of the unconditioned stimulus (US) with which it was associated during learning can trigger two opposing memory mechanisms [1,2]. If the retrieval event is brief, the original memory becomes labile and sensitive to amnestic agents, and requires reconsolidation in order to be restabilised in the brain. By contrast, if the retrieval cue is presented repeatedly or for a long period of time in the absence of the reinforcer, extinction occurs through the formation of a new associative CS-noUS memory, termed an 'extinction memory'. These two memory processes triggered by retrieval have opposite outcomes at the behavioural level. While the conditioned response is maintained after reconsolidation [3], extinction inhibits the expression of the original memory [4]. Hence, depending on retrieval conditions the control over behaviour by the CS will be determined by the dominant memory trace, either the original CS-US or a newly formed CS-noUS extinction memory [5].

The fact that fully consolidated memories can undergo reconsolidation at retrieval provides a unique opportunity to alter the content of the CS-US association in healthy or unhealthy individuals. Preventing or delaying forgetting, and improving the accuracy and persistence of associative memories could have a direct and positive impact on cognition. In healthy individuals and, more speculatively, in those with neurodegenerative diseases who experience memory decline, hypermnestic treatments given during reconsolidation, or simply engaging and exploiting the reconsolidation process itself may enhance memory or prevent its progressive decline. Maladaptive, intrusive memories characterize post-traumatic stress disorder (PTSD) and also drug addiction, whereby drug CSs can elicit subjective cravings and relapse to drug use. Diminishing the impact of traumatic memories has been proposed as a novel approach to treating PTSD, bringing benefits of improved cognition in those whose lives and behaviour are adversely affected by powerfully aversive memories [6]. By diminishing the propensity to use drugs through the diminution of drug memories that elicit drug use [7] improvements in cognition seen in, and that likely contribute to continuing, abstinence [8-10] may be facilitated. Thus, the disruption of maladaptive memories by using amnestic agents during reconsolidation offers an opportunity for preventing further decline, recover or even enhance cognitive capacities.

Here we will review recent studies in human and non-human animals on the impact of manipulating associative memories at reconsolidation. We discuss the boundary conditions for

retrieval to trigger reconsolidation and how this event can influence the fate of memories. Then we discuss the effects of behavioural or pharmacological manipulations during the reconsolidation of declarative and non-declarative memories.

2. Memory fate after retrieval

Dissociation between memory retrieval and reconsolidation. Depending on their strength, long-term memories are stably stored in the brain from days up to the entire life of an individual. Accumulating evidence indicates that memory retrieval induced by a cue-reminder labilises the engram which must undergo restabilisation in order to persist in the brain [11]. The return to a labile state renders memories sensitive to a variety of amnestic agents, such as protein synthesis inhibitors [12]. The successful engagement of this so-called reconsolidation process by retrieval requires a 'violation of expectations', or a mismatch, between what occurs and what was expected according to the original CS-US association, often now referred to as a prediction error. The first evidence that this mismatch was necessary for retrieval to induce reconsolidation was obtained in the crab *Chasmagnathus* using an aversive context-signal memory (CSM) procedure in which a visual danger stimulus (VDS) was associated with a specific training context. Once the CSM was fully consolidated, brief exposure to the training context (CS) without the VDS triggered reconsolidation, as demonstrated by the sensitivity of the memory to the protein synthesis inhibitor cycloheximide. By contrast, if the brief context exposure terminated with presentation of the VDS – allowing for successful retrieval of the CSM, but no mismatch or prediction error – then cycloheximide had no amnestic effect [13]. Similar observations were made in human volunteers who had undergone fear conditioning; retrieval of the CS-US memory only engaged reconsolidation when there was a prediction error, which was varied by either increasing or decreasing the contingency between the CS and shock US. As for cycloheximide in crabs, the β-adrenoreceptor antagonist, propranolol, prevented reconsolidation of the fear memory, but only when the retrieval conditions embodied a prediction error, and not when CS-induced retrieval was followed by US presentation [14]. These observations along with similar findings for spatial memory in rats [15] and a declarative memory in humans [16], suggest that engaging reconsolidation is not inevitably a consequence of memory retrieval, and destabilization of the memory requires a failure in memory prediction.

Another two factors that influence the capacity of retrieval to induce reconsolidation are memory age and strength. Experimental evidence in auditory fear conditioning and morphine-

conditioned place preference in rats suggests that stronger memories are more resistant to the induction of reconsolidation [17,18]. Thus the stronger the memory, the more numerous or extensive CS presentation must be in order to engage reconsolidation. Furthermore, increasing the interval between training and reactivation also reduces the likelihood of engaging reconsolidation. As with increased memory strength, after a longer delay emotional or declarative memories become resistant to reactivation [19,20], and a greater exposure to the CS (longer duration and/or more presentations) is required to trigger memory reconsolidation [19].

Not only are there boundary conditions that determine whether reconsolidation is engaged by retrieval, but also the processes of retrieval, destabilisation and restabilisation depend upon specific and dissociable glutamate receptor-mediated mechanisms. Thus, using selective agents infused directly into the basolateral amygdala (BLA), it has been shown that memory retrieval depends on AMPA-type glutamate receptors, destabilisation of the trace requires glutamate transmission at GluN2B-containing NMDA receptors, while restabilisation itself depends on GluN2A-containing NMDA receptors [21]. In several types of associative memories, retrieval blockade by AMPAR antagonists, although preventing the behavioural manifestation of memory (avoidance of an aversive conditioned taste, freezing to a fear CS or reduced exploration of a known object) did not prevent memory labilization or reconsolidation [21-23].

Taken together, these data imply that memory retrieval is not an unequivocal indication of memory labilization and reconsolidation. Studies using a wide range of animals (from invertebrates to humans) and memory types (declarative and non-declarative) reveal that reconsolidation is a universal property of associative memory processing and persistence, but that the conditions under which this process is engaged are rather constrained.

Dynamic relationship between reconsolidation and extinction. Another behavioural consequence of an unrewarded CS presentation is memory extinction. While a brief CS exposure triggers reconsolidation, prolonged or repeated cue exposure leads to extinction and the formation of a new inhibitory associative memory (CS-noUS). However, in rats with a fully consolidated fear memory, an intermediate number of CS presentations failed to engage either reconsolidation or extinction, suggesting that these two processes are both mutually exclusive and also separated by a phase of insensitivity, or ‘limbo’, when neither is occurring [24]. Similarly, fear memory in humans also shows an insensitive phase following an intermediate

number of CS presentations, suggesting that this apparent 'limbo' state represents a conserved property in associative memory processing [25].

At a mechanistic level, reconsolidation and extinction show similarities and differences. Fear memory reconsolidation requires, among other processes, *de novo* protein synthesis, NMDA-glutamate receptor activity (NMDAR) and extracellular-signal regulated kinase 1/2 (ERK1/2) activation in the BLA [12,26,27]. In addition to these same molecular mechanisms, fear extinction requires *de novo* synthesis of the Ca^{2+}/calmodulin-dependent protein phosphatase calcineurin in BLA [24,27,28].

Therefore, specifically triggering memory reconsolidation requires exposure to a precise number of CS reminder cues depending upon the strength and age of the memory and the generation of a prediction error at reactivation. Furthermore, given that the same pharmacological manipulation (e.g. treatment with an NMDAR antagonist) will affect memory persistence in opposite ways depending on whether reconsolidation or extinction is engaged, understanding this relationship for different types of associative memories will be important in order specifically to target memory content and persistence in a clinical environment.

3. Enhancing cognitive function by reactivation-dependent memory manipulations

Enhancement of memory features by reconsolidation. Several examples from the last decade show that the reconsolidation of fully consolidated associative memories can modify some of their properties, including their persistence, accuracy and specificity.

In rats, reactivation of an inhibitory avoidance (IA) memory many days after training, by presenting a brief reminder session, triggers a long-lasting reconsolidation-mediated increase in memory strength and persistence observed at test in comparison to animals not having undergone reactivation [29,30]. This enhancement required the participation of multiple brain regions including the amygdala, hippocampus and medial prefrontal cortex [30]. The forgetting that may occur with the passage of time can also be reduced by memory reactivation. For example, contextual fear memory reactivation by exposure to the training context 35 days after training prevented forgetting of the association as indicated by an increase in memory generalization at remote time points [31]. Moreover, weekly reactivation sessions during the month following conditioning maintained the capacity of animals to discriminate between a

training and a novel context [32]. These observations in rats clearly support a strengthening effect of reconsolidation on hippocampus-dependent associative memories.

Reconsolidation-induced memory improvement has also been demonstrated for a hippocampus-dependent declarative memory in humans [33,34]: one or two consecutive reminder events triggered reconsolidation and strengthened a subsequently retrieved declarative word list-memory and maintained the memory for a longer period of time. Interestingly, this strengthened memory was also more resistant to interference from other word lists [34]. However, reactivating a remote declarative memory, while labilising the trace and thereby making it sensitive to interference, did not result in a memory strengthening effect [34]. It has been reported that personal (episodic) memories can be selectively enhanced or distorted in a reactivation-dependent manner [35]. However, enhancement was achieved by matching reactivation-encoding conditions rather than mismatching them to generate a predicition error which might instead indicate that retraining, rather than reconsolidation enhancement, could be a significant factor in the results of these experiments.

Real life events, such as exposure to mild stressors, during the memory reconsolidation process can also enhance associative memories. For example, in crabs, an episode of water deprivation that increases central angiotensin-II levels, positively modulated a contextual memory if this physiological stress effect occurred during the reconsolidation window [36]. Similarly, human declarative memory is enhanced when reconsolidation takes place in the presence of a cold pressor stress that induces a reliable stress hormone response [37].

Pharmacological interventions concurrent with reconsolidation can also act as memory enhancing treatments. In rats, systemic or intra-BLA administration of the NMDAR partial agonist D-cycloserine, in conjunction with memory reactivation, enhanced fear to an auditory cue at a later test when compared with the saline-treated, reactivated control [27]. Post-reactivation systemic injections of nicotine enhanced a contextual fear memory in rats in a reactivation- and dose-dependent manner [38]. Interestingly, pharmacological manipulations at reconsolidation can also rescue a memory from an interference manipulation that would normally disrupt it. Intra-hippocampal administration of the acetylcholine precursor and α7-containing nicotinic acetylcholine receptor agonist choline, immediately after contextual memory reactivation led to the recovery of young (2-7 days old) but not old (21 days old) memories when individuals had been subjected to interference induced amnesia [39].

Overall there is clear evidence in human and non-human animals for a role of reconsolidation in enhancing some aspects of memory such as resistance to forgetting, accuracy and specificity. A brief memory reactivation episode alone, or in combination with pharmacological interventions, may provide a promising approach to preventing the decline of, or even enhancing, fully consolidated, non-declarative or declarative memories in humans. Seen on the background of the utility of engaging in memory tasks in individuals with memory loss associated with neurodegenerative diseases, it may be of value to implement reconsolidation manipulations in the early stages of such disorders and thereby prevent or delay memory related cognitive impairments (Figure 1A).

Disruption of maladaptive memories by reconsolidation manipulations. Despite an abundant animal literature showing disruption of fear memory reconsolidation, only a few studies have approached this subject in humans, especially those with neuropsychiatric disorders. The widely prescribed antihypertensive drug, propranolol - a β-adrenoreceptor antagonist - has been shown in healthy volunteers to prevent fear memory reconsolidation [40], as it does in animal studies [41]. Propranolol treatment immediately before fear memory reactivation, achieved by brief exposure to the fear CS alone, reduced fear expression 24 hours later. This effect was specific to expression of the reflexive emotional component of the fear response (fear-potentiated startle), without affecting the capacity of the participants to recollect the fear conditioning event on previous days and hence the expectancy that they would receive an electric shock. Moreover, a hippocampus-dependent emotional memory was also disrupted by propranolol at reactivation, but again had no effect on the episodic memory component, instead preventing the modulatory influence of the amygdala on memory reconsolidation [42]. This distinction between reconsolidation-dependent disruption of emotional versus episodic components of an aversive (fear) memory is important as there is little or no evidence in the human experimental literature that episodic memories undergo reconsolidation at reactivation: there is no ‘eternal sunshine of the spotless mind’. Thus, individuals undergoing emotional memory reconsolidation blockade subsequently show reductions in their emotional response to the CS, but do not experience loss of their memory of the original event underlying the establishment of the memory. This pattern of amnesia would be very useful in a clinical setting, as the loss of the emotional response to trauma is the desired clinical outcome, rather than a loss of the memory for the trauma in itself. There have been attempts to translate these findings on fear memory reconsolidation in animals and humans to the clinical context of PTSD with

promising preliminary results with propranolol given at retrieval resulting in reduced autonomic responses during subsequent retrieval episodes, at least in small-scale human experimental medicine trials [43,44]. Replication and extension of these results in fully controlled clinical trials is therefore warranted.

The animal literature indicates that reconsolidation manipulations may also have promise in treating neuropsychiatric disorders other than PTSD, with a large amount of evidence suggesting utility in treating drug addiction. In individuals addicted to drugs, especially those that have achieved abstinence for sometimes prolonged periods of time, exposure to drug-associated cues can elicit drug cravings and relapse to drug seeking and taking [45-47]. In animal models of drug seeking and relapse, propranolol or an NMDA receptor antagonist given at drug cue-induced memory reactivation profoundly decreased drug seeking responses to those same drug cues in subsequent tests [48-52], suggesting an approach to promoting abstinence through the diminution or erasure of drug-associated memories [7,53]. The importance of enhancing the likelihood of abstinence, which is a difficult outcome in addiction treatment, is important not only in its own right, but because of the evidence that cognitive and decision-making impairments associated with the addicted state [54-56] are ameliorated [10] and this may further enhance the ability of vulnerable individuals to respond positively to behavioural, including mindfulness, therapeutic interventions (Figure 1B).

There have been few clinical studies to date that have reported on this approach, but a preliminary study has shown that in cocaine-dependent individuals, propranolol administered following cocaine cue exposure resulted in a significant attenuation of craving and cardiovascular reactivity to the drug cue at a later test [57].

An alternative approach to memory reduction or erasure is to combine brief reactivation of the memory (as used in reconsolidation procedures) with extinction training, i.e. multiple exposures to a non-reinforced CS within the reconsolidation window – a period that can extend to about 4h after reactivation. This ‘super-extinction’ has been demonstrated for fear memory in rats [58] and in human subjects, when reduced cue-induced fear responses were apparent for up to a year after the retrieval-extinction procedure [59]. Although the mechanisms underlying this apparent erasure, or overwriting, of the original memory are unclear, the original memory does appear to be affected, as indicated by the absence of renewal or reinstatement of the fear memory that is usually seen following extinction alone [58,59]. This procedure has somewhat remarkably also been demonstrated in rats self-administering cocaine and heroin and in a

population of heroin-addicted inpatients [60]. Reactivation of a drug memory by showing a short video of drug use, followed by longer exposure to the same video (the extinction training), with the two being separated by 10 minutes resulted in a long-lasting reduction in autonomic responses to subsequent drug cue presentations, drug craving and successful abstinence [60]. Replication of these important results, and extension to other drug addict populations would be an important clinical advance.

Key importance of retrieval parameters when targeting reconsolidation. As has been emphasised above, the effective CS presentation conditions that define the engagement of reconsolidation or extinction are significantly affected by the age and strength of a memory and, critically, the memory reactivation characteristics. Since pharmacological treatments that disrupt reconsolidation can also disrupt extinction [27], selecting the optimal reactivation parameters effectively to engage reconsolidation rather than extinction, or an insensitive state [24], is critical in achieving the desired memory outcome. Similarly, treatments that can enhance reconsolidation, such as NMDA receptor agonists, can also enhance memory extinction leading to a stronger inhibitory memory [27]. This is illustrated by two studies in which D-cycloserine was given in association with cocaine cue exposure in order to enhance extinction of a drug memory, but the outcome was instead an increase in the response to cocaine cues measured at a later time point, the opposite of that expected [61,62]. It is entirely possible that this result is explained by enhancement of the reconsolidation of the drug memory because the parameters of cocaine cue exposure were insufficient to engage the extinction process, as has previously been shown in rats [27].

4. Conclusion

A growing body of experimental evidence suggests that fully consolidated associative memories can undergo reconsolidation and that the memory can both be diminished and enhanced by pharmacological, cognitive and behavioural manipulations. On the one hand, reconsolidation of useful memories alone or in presence of facilitatory manipulations (e.g. real life events, memory enhancers) can delay forgetting, increase memory persistence and resistance to interference, and maintain accuracy and specificity. On the other hand, the data

suggest that this approach may also have therapeutic value in the treatment of neuropsychiatric disorders in which maladaptive emotional memories play a key role.

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Legend

Figure 1: Effect of memory reconsolidation manipulations on cognition. A. The acquisition of an associative memory supports specific memory-dependent cognitive capacities. A reconsolidation episode (green arrow) can strengthen the original memory, enhancing cognition. Reconsolidation alone, or in combination with hypermnestic treatments, of declarative and non-declarative memories has been shown to be an effective manipulation to maintain or prolong memory accuracy, specificity and strength. **B.** The establishment of maladaptive long-term memories (LTM), a common characteristic in conditions such as PTSD or drug addiction, compromise cognitive performance. Disrupting these associative memory components (purple arrow) by pharmacological disruption of memory reconsolidation offers an opportunity to reduce the impact of these memory traces and thereby lead to improvements in cognition.

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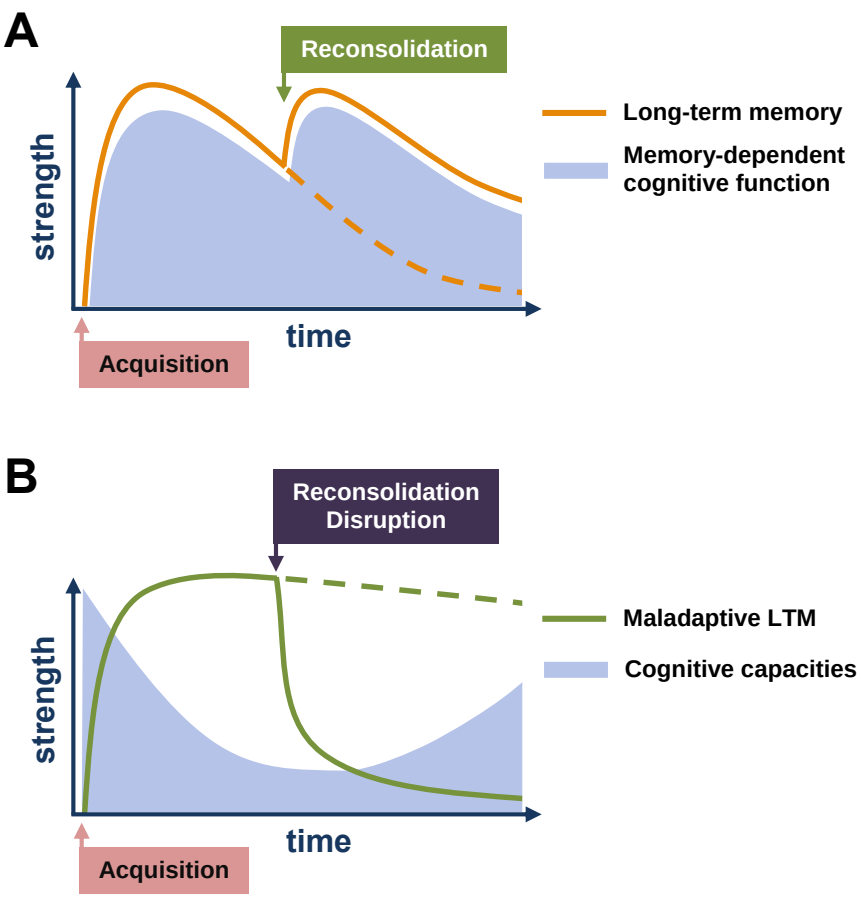
A
Reconsolidation
strength
time
Acquisition
Long-term memory
Memory-dependent
cognitive function
B
Reconsolidation
Disruption
strength
time
Acquisition
Maladaptive LTM
Cognitive capacities