The chains of habits: too strong to be broken by reconsolidation blockade?

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Abstract

Memory reconsolidation – the process by which memories can become destabilised at retrieval, and be updated or modified – offers a potential therapeutic opportunity for mental health disorders based upon maladaptive emotional memories, such as drug addiction. Blocking the reconsolidation of pavlovian cue-drug memories persistently reduces subsequent relapse in rodent models and in human experimental medicine studies, but little is known about whether instrumental drug-seeking memories can be disrupted, particularly when individuals have transitioned to a compulsive drug-seeking habit. Here we discuss how studies of drug memory reconsolidation can be made more translationally relevant, with particular attention to the challenges faced by those attempting to disrupt the reconsolidation of habit memories.

Highlights

- Maladaptive memories underlie drug-seeking habits and lead to relapse in addiction.
- Reconsolidation might be exploited to disrupt maladaptive memories.
- Disrupting the reconsolidation of cue-drug memories reduces relapse.
- Though debatable, instrumental memories likely do reconsolidate.
- Habit memories may pose challenges for reconsolidation blockade therapies.

Introduction

Memory reconsolidation is the process by which well-consolidated long-term memories can become malleable and vulnerable to amnestic agents under certain conditions of retrieval [1,2]. Briefly, previously consolidated memories can exist in either a stable 'inactive' state, or an unstable 'active' state, with retrieval or reactivation of the memory returning it from the consolidated inactive state to the labile active state (**Figure 1**). This process does not occur each time that a memory is retrieved, but rather is selectively engaged when there is novel information to integrate into the memory trace; more formally, when a prediction error is generated at reactivation [3]. This latter finding has contributed to the view that reconsolidation exists to update old memories [4].

Shortly after the rediscovery of reconsolidation, speculation began that reconsolidation might be exploited to provide a therapeutic tool for mental health disorders characterised by excessively intrusive or controlling memories. Essentially, it was reasoned that if old, well-consolidated, maladaptive emotional memories contribute to the persistence of a mental health disorder, then reactivating those memories should render them once again susceptible to disruption with an amnestic agent, much as the initial consolidation of memory can be disrupted if amnestic agents are applied shortly after learning. Initial work in rodent models indicated promise for this strategy in the treatment of post-traumatic stress disorder [5] and drug addiction [6], the latter being the focus of this review. However, while progress into human clinical populations has been steadily advancing for the treatment of post-traumatic stress disorder [7,8,though see 9 for a failure to replicate], the treatment of addiction has been much slower and more challenging. Here, we consider the additional challenges faced by reconsolidation approaches to treating addiction. After summarising some key studies of drug memory reconsolidation, we discuss the potential difficulties in translating this research to the clinic. Firstly, we will address whether the extent of drug self-administration training used in studies of drug memory reconsolidation is suitably reflective of patterns of acquisition seen in drug addiction. Secondly, we will describe the distinct neural and

psychological processes engaged after extended periods of drug-seeking and how reconsolidation research conducted to date has typically not acknowledged these differences, despite their hypothesised role in drug addiction [10]. Finally, we consider instrumental memory reconsolidation, particularly those memories that likely underlie substance use disorders, and the specific challenges that these might pose for the development of reconsolidation-based therapies.

Initial studies of drug memory reconsolidation: focus on maladaptive pavlovian associations

Drug addiction is arguably a disorder of maladaptive emotional memories [11], with both pavlovian and instrumental memories contributing to its persistence, and continued high risk of relapse. It is well-established in the clinical and preclinical literature that environmental cues (e.g. people, places and paraphernalia associated with drug use) can become conditioned stimuli (CSs) associated to the drug high, subsequently becoming potent precipitators of relapse during abstinence. Thus, a number of investigators reasoned that disrupting the reconsolidation of these memories – i.e. inducing their reactivation and administering an amnestic agent – might provide a novel therapeutic strategy that could persistently reduce the risk of relapse. The first studies investigating this hypothesis were published over a decade ago [6,12] using rodent models of addiction utilising intravenous cocaine self-administration and experimenter-administered cocaine conditioned place preference respectively; here, in the interests of space and their likely increased relevance to substance use disorders, we focus on rodent models using drug self-administration procedures.

The earliest studies investigating the susceptibility of drug-associated memories to disruption at reconsolidation focused on targeting the plasticity-related immediate early gene *zif268*, which had previously been shown to be upregulated in response to exposure to drug-associated cues [13]. Selective knockdown of *zif268* using antisense technology within the basolateral amygdala prior to memory reactivation was shown to subsequently reduce the capacity of the drug-associated CS to act as a conditioned reinforcer [6] and to prevent CS-maintained drug-seeking behaviour in

more translational models of relapse [14]. The upregulation of *zif268* was subsequently shown to depend upon activation of the NMDA receptor [15], most likely mediated through the activation of intracellular protein kinase signalling pathways such as ERK [16] and PKA [17], although a direct causal link still remains to be demonstrated.

Increasing the potential impact of reconsolidation blockade

Although providing proof-of-principle that a reconsolidation blockade approach may be useful for developing new treatments for drug addiction, the approach taken in the initial studies of drug memory reconsolidation could be made more translationally relevant in several ways.

Increasing the extent of drug exposure

The length of drug exposure in the intravenous drug self-administration procedures used in reconsolidation studies is typically 10-12 days, with approximately 200-500 CS-drug pairings [14,15,18-22]. While an improvement on experimenter-administered drug procedures such as conditioned place preference (typically 4-8 drug exposures), it is estimated that the average length of exposure in human drug users is considerably longer, and the number of CS-drug pairings approximately 300 times greater [23]. This is a potential concern because the extent of training has been shown to affect the propensity of a memory to reconsolidate. In pavlovian fear conditioning, which can be learned with a single CS-shock pairing, strong training occurring as a result of 3 pairings results in a greater resistance of the memory to destabilisation [24]. Although in the drug self-administration literature reconsolidation deficits have been observed with large numbers of CS-drug pairings during training [15,18-21], it is not clear how to compare the strength of memory induced by a single CS-shock pairing and that induced by a single CS-drug pairing. Whilst it is possible that the extent of training for appetitive memories has less of an impact on memory destabilisation than for fear memories, it is also possible that appetitive training procedures have not yet reached sufficient

numbers of CS-reinforcer pairings to observe the 'boundary conditions' on reconsolidation that have been reported in the fear literature.

Secondly, the extent of training also affects both the psychological and neurobiological underpinnings of drug-seeking behaviour. During the development of drug addiction, both instrumental and pavlovian drug-relevant memories become maladaptive [11]; in particular, addiction is hypothesised to depend upon the transition from 'goal-directed' to 'habitual' instrumental drug-seeking and drug-taking behaviour [10]. This transition depends on several factors; most notably the extent of training, with prolonged training promoting the formation of habits [20]. For example, it is well-established that instrumental responding for food, while initially governed by direct associations between the action and the reinforcer (i.e. 'action-outcome', or 'goal-directed' associations) becomes, after extended training, independent of reinforcer value [25]. These 'stimulus-response' or 'habitual' associations maintain responding even if the reinforcer has been devalued, e.g. after excessive pre-feeding on that reinforcer, or if the reinforcer has recently been associated with illness. This is not the case for goal-directed behaviour, where responding would be reduced by either of these two experiences. Importantly, drug exposure itself can accelerate the transition between goal-directed and habitual responding [26,27].

The transition from goal-directed to habitual behaviour in addiction is linked to shifts in the neural, particularly striatal, circuitry underlying drug-seeking and drug-taking behaviour. It has long been known for natural reinforcers that this transition recruits different parts of the striatum [28,29] and this also appears to be the case for drug reinforcers, as shown by the use of second-order schedules of reinforcement (see [30] for review). It has been shown that early in instrumental training, when drug-seeking is most likely goal-directed, infusion of dopamine receptor antagonists in the dorsomedial striatum [31] or GABA receptor agonism within basolateral amygdala [32] reduces drug-seeking behaviour maintained by drug-associated cues. By contrast, when animals are responding under second-order schedules of reinforcement after extensive training (when the

behaviour is more likely habitual), these manipulations are no longer effective. However, dopamine receptor antagonism and GABA receptor agonism in the dorsolateral striatum [31,33,34] and central nucleus of the amygdala [32], respectively, produce impairments in cue-maintained seeking behaviour at these later time points, but not earlier. These double dissociations likely reflect a shift in the striatal and amygdala circuitry that is indicative of the transition from goal-directed to habitual drug-seeking behaviour.

Because of its critical role in assigning affective value to pavlovian CSs [35], most of the drug memory reconsolidation literature has focused upon targeting the BLA with amnestic agents at reactivation to reduce subsequent drug-seeking behaviour. However, given that after extensive training, cue-maintained drug-seeking behaviour is no longer dependent on this region [32], it is not clear whether manipulations such as *zif268* knockdown in the BLA would be effective in disrupting the influence of pavlovian CSs on habitual behaviour, or whether reactivation of the memory would lead to a second period of dependence on the BLA, similar to that observed for the hippocampus with the systems-level reconsolidation of fear memories [36].

Interestingly, administration of the mTOR inhibitor rapamycin directly to the central nucleus of the amygdala, in conjunction with a memory reactivation session, has been shown to reduce alcohol-seeking in rats [37] – consistent with recruitment of a central amygdala pathway as habits develop. In this study, no response-contingent cues were used during training, suggesting that the instrumental, rather than a pavlovian, drug memory was being disrupted. However, the amnestic effects of rapamycin did not appear to depend on execution of the operant response in the memory reactivation sessions, as would be expected if this were the case; rather, presentation of a non-intoxicating dose of alcohol destabilised the memory [37]. Therefore, while this demonstrates that it is possible to disrupt reconsolidation by targeting amygdala subregions other than the basolateral nucleus, the central-amygdala-dependent nature of the amnestic effect does not necessarily show that a habit memory has been disrupted. Alternatively, the dependence of the memory on the

central amygdala may reflect the more generalised, contextual encoding that is observed for alcohol as compared to other reinforcers [38,39].

Targeting drug-seeking habit memories

The question of whether *instrumental* memories – goal-directed or habitual – reconsolidate has been a challenge since the earliest days of re-emergence of reconsolidation research. Although initial studies suggested that instrumental memories did not reconsolidate [40], more recent work has suggested that these memories do, in fact, destabilise under appropriate reactivation conditions [41,42]. However, the capacity of drug-seeking *habit* memories to reconsolidate is questionable for a number of reasons: (i) the nature of training required to generate habit memories may cross the boundary conditions limiting memory reconsolidation; (ii) as discussed above, habitual behaviour recruits separate corticostriatal circuitry, which has been little investigated in the context of reconsolidation compared to the 'goal-directed circuitry', and; (iii) theoretically, because habit memories are rigid (i.e. are not sensitive to changing contingencies or reinforcer value) then it is questionable as to how sufficient prediction error could be generated to induce a habit memory to destabilise. The paucity of published papers on habit memory reconsolidation, when it has been widely acknowledged that disrupting maladaptive habits would be beneficial for the treatment of drug addiction, speaks to the difficulty of targeting habit memories using reconsolidation procedures.

One of the defining features of a habit memory is its 'stimulus-response' nature, and that responding is independent of the outcome of an individual learning trial or ultimate goal desired by the individual. It has also been suggested that the development of compulsive habits is key in the transition from drug abuse to drug addiction [10], with the insensitivity of habitual behaviour to changes in outcome leading to the insensitivity to punishment that characterises addictive behaviour [43,44]. From this perspective, it might seem unlikely that there could be a sufficient 'violation of

expectations' at reactivation [45] to induce habit memories to destabilise and so become susceptible to disruption with amnestic agents.

However, perhaps counterintuitively considering the rigid nature of the behaviour, it is possible to overcome habits (though not necessarily *compulsive* habits). Whilst the reconsolidation of associations between conditioned stimuli and their reinforcers has received extensive attention, the reconsolidation of the stimulus-response memory itself has been less explored. Computational neuroscience indicates that the formation (and therefore perhaps the re-formation) of habit memories depends upon prediction error. In computational terms, the formation of habits reflects a 'model-free' system in which learning occurs through temporal-difference learning rules [46], with the system estimating the likelihood of reward following an action by aggregating evidence from previous performances of that action and, if appropriate, updating the estimate based on a reward prediction error signal. Since the late 1990s, it has become increasingly accepted that dopamine provides the neurochemical basis for the reward prediction error signal (see [47] for review). In light of the requirement for prediction error in the destabilisation of memories [3,45], recent work has investigated the neurochemical basis of pavlovian appetitive memory destabilisation, and also found it to be dopaminergic [48,49]. This suggests that destabilising habit memories may be possible, so long as appropriate reactivation parameters – inducing sufficient prediction error – can be identified.

One study [42] investigating instrumental memory reconsolidation in detail determined that changing the contingency of reinforcement at reactivation, from a predictable fixed ratio schedule to a less predictable variable ratio schedule, allowed a well-learned instrumental memory to reconsolidate. By comparison, omitting reinforcement altogether during reactivation was not effective at inducing memory destabilisation. This finding illustrates the delicate balance in designing memory reactivation sessions; the session must be sufficiently different from the original training to induce the prediction error necessary for destabilisation of the memory, whilst not being *so* different that the session is perceived as a new training experience. While much more research is required to

determine the fundamental principles that allow the generation of appropriate and sufficient prediction error for memories to destabilise (and therefore a logical approach to designing memory reactivation sessions), this suggests that inducing the destabilisation of memories is a practical problem to be solved, rather than a theoretical issue that cannot be overcome.

Conclusions

It has been over a decade since the first demonstrations that drug memories undergo reconsolidation, and the suggestion was made that targeting reconsolidation might provide a novel form of treatment for drug addiction. While much has been discovered regarding the neural, neurochemical and molecular mechanisms underlying pavlovian memory reconsolidation, investigations of habit memory reconsolidation have been more difficult, due to the technically demanding nature of these studies and the difficulty in designing effective memory reactivation sessions. However, while the disruption of habitual drug-seeking memories may be an ultimate goal for applied memory reconsolidation research, until that goal is reached there appears to be value in disrupting reconsolidation to prevent the influence of pavlovian cues on relapse behaviour, as shown by experimental medicine studies conducted with human heroin users [50] and those classed as hazardous alcohol drinkers [51].

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Figure legends

Figure 1 Through the process of reactivation-induced destabilisation, consolidated memories can once again enter an active state, permitting incorporation of novel information into the memory trace. During this period of reactivation memories are maintained by instable memory mechanisms and are returned to their inactive, stable state, through the process of reconsolidation. Preventing the restabilisation of the unstable memory through the use of amnestic agents has been suggested as a potential form of memory disrupting treatment for mental health disorders such as drug addiction.