New Approaches for Alcohol Use Disorder Treatment via Memory Retrieval and Reconsolidation Manipulations

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Abstract Relapse to alcohol seeking and drinking is a major clinical challenge in alcohol use disorder and is frequently brought about by cue-induced craving, caused by exposure to cues that evoke alcohol-related memories. It has been postulated that memories become labile for manipulation shortly after their retrieval and then restabilize in a "memory reconsolidation" process. Disruption or interference with the reconsolidation of drug-associated memories has been suggested as a possible strategy to reduce or even prevent cue-induced craving and relapse. Here, we review literature demonstrating the capacity of behavioral or pharmacological manipulations to reduce relapse in animal models and humans when applied after a short retrieval of memories associated with alcohol, suggestively disrupting the reconsolidation of such memories. We suggest that while there is a clear potential of using post-retrieval manipulations to target specific relapse-evoking memories, future research should be more systematic, standardized, and translational.

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Specifically, we discuss several critical limitations and boundary conditions, which should be addressed to improve consistency and replicability in the field and lead to the development of an efficient reconsolidation-based relapse prevention therapy.

Keyword Addiction · Alcohol · Animal models · Aversion therapy · Counterconditioning · Memory reconsolidation · Memory retrieval · Relapse

1 Introduction

Alcohol use disorder (AUD) is a relapsing disorder. Even with successful pharmacological and/or psychological treatment, 60–70% of patients relapse within the first year of abstinence (Sinha 2011; Witteman et al. 2015). Pharmacotherapy that is available for AUD is very limited and is not effective for relapse prevention. Relapse to alcohol abuse is often triggered by craving, induced by exposure to environmental cues previously associated with the reinforcing properties of the drug (Niaura et al. 1988; Bouton 2002; Witteman et al. 2015; Venniro et al. 2016). Therefore, disruption or attenuation of the cue-alcohol associative memories is expected to reduce cue-induced craving and relapse.

It has been increasingly accepted over the past two decades that the retrieval of consolidated memories induces their temporal destabilization, which is followed by their restabilization in a process termed "reconsolidation" (Nader and Hardt 2009; Lee et al. 2017). Certain pharmacological manipulations applied following memory reactivation via retrieval of that memory can attenuate the subsequent behavioral expression of the target memory. This was taken as evidence of the disruption of the ongoing reconsolidation process (Przybyslawski et al. 1999; Nader et al. 2000; Barak and Goltseker 2021). Thus, the term "reconsolidation window" was proposed, implying that interference with memory reconsolidation during this 5–6 h window of opportunity can attenuate the retrieved memory (Nader and Hardt 2009; Lee et al. 2017).

Research on such memory flexibility has been applied in the drug addiction field (both preclinically and clinically). Accordingly, it has been shown that interference with the reconsolidation process could attenuate and even prevent relapse to drug seeking and consumption (Valjent et al. 2006; Barak et al. 2013; Dunbar and Taylor 2017; Exton-McGuinness and Milton 2018; Goltseker et al. 2019; Taujanskaite et al. 2020; Barak and Goltseker 2021). Drug seeking or intake has also been attenuated by applying competing novel learning shortly following memory retrieval, suggested to reflect the incorporation of new information into the retrieved memory trace (Gordon 1977; Monfils et al. 2009; Schiller et al. 2010; Auber et al. 2013; Olshavsky et al. 2013; Goltseker et al. 2017, 2021; Lee et al. 2017; Paulus et al. 2019; Barak and Goltseker 2021).

This review surveys preclinical and clinical studies addressing manipulations applied in conjunction with retrieval of alcohol-associated memories, together

aimed at reducing relapse-related behaviors. Most of these studies, conducted in animal models and in human subjects, were considered within the theoretical framework of "memory reconsolidation." This review indicates that alcohol-associated memories can potentially be disrupted by post-retrieval manipulation, possibly due to interference with the reconsolidation process, leading to reduced relapse. However, given the theoretical debates, replicability issues, and inconsistency that currently characterize the field (Barak and Goltseker 2021), this review also discusses several points that should be considered for future studies on reconsolidation-related topics in general, and those related to alcohol and drugs of abuse in particular.

2 Pharmacological Interference with Alcohol Memory Reconsolidation

Memory reconsolidation has been shown to depend on de novo protein synthesis, as protein synthesis inhibitors have been repeatedly shown to disrupt the behavioral expression of a memory (typically, responses to a cue) (Nader et al. 2000; Lee et al. 2017). Other pharmacological interventions were also shown to disrupt memory reconsolidation, in particular, NMDA and β-adrenergic receptor blockade (Lee et al. 2017).

The same pharmacological targets have also been investigated as potential targets for disrupting alcohol memory reconsolidation (Barak and Goltseker 2021). Thus, pharmacological studies on alcohol-associated memory reconsolidation have focused on protein synthesis inhibition (von der Goltz et al. 2009; Barak et al. 2013; Lin et al. 2014), β-adrenergic receptor (Wouda et al. 2010; Font and Cunningham 2012; Milton et al. 2012; Lonergan et al. 2016; Schramm et al. 2016; Chesworth and Corbit 2018), and NMDA receptor blockade (von der Goltz et al. 2009; Wouda et al. 2010; Milton et al. 2012; Vengeliene et al. 2015; Puaud et al. 2018; Das et al. 2019).

2.1 Protein Synthesis Inhibition

The most consistent and well-established finding in memory reconsolidation studies is that the protein synthesis inhibitors administered after memory reactivation disrupt the behavioral expression of a memory, pointing to a role for protein synthesis in the reconsolidation process (Nader and Hardt 2009; Lee et al. 2017; Taujanskaite et al. 2020). However, only a few studies have tested the role of protein synthesis in the reconsolidation of alcohol-related memories. For instance, intracerebroventricular administration of the protein synthesis inhibitor anisomycin after memory retrieval (a 5-min extinction session) disrupted alcohol seeking in an operant self-

administration paradigm for at least a week (von der Goltz et al. 2009). Similarly, injection of anisomycin into the central amygdala (CeA) following memory retrieval reduced alcohol seeking and self-administration (Barak et al. 2013).

The crucial involvement of protein synthesis in the reconsolidation of alcohol-associated memories came with the demonstration of the role of the mammalian (mechanistic) target of rapamycin complex 1 (mTORC1) pathway in memory retrieval and reconsolidation (Barak et al. 2013). mTORC1 is a kinase that plays a role in the translation of a subset of proteins, including synaptic proteins, and has been implicated in synaptic plasticity and in learning and memory (Hoeffer and Klann 2010; Neasta et al. 2014). The retrieval of alcohol-associated memories induced activation of the mTORC1 pathway in the CeA, and in the orbitofrontal and prelimbic cortices, which led to increased levels of several synaptic proteins for which expression is regulated by mTORC1 (Barak et al. 2013). Systemic or intra-CeA administration of the mTORC1 inhibitor rapamycin (20 mg/kg) following alcohol memory retrieval disrupted the reconsolidation of alcohol-related memories, leading to long-lasting (14 days) suppression of relapse to alcohol consumption. Critically, when rapamycin was injected 5 h after memory retrieval, it had no effect on subsequent relapse, indicating that mTORC1 inhibition should be conducted shortly after memory retrieval, i.e., within the "reconsolidation window."

Interestingly, alcohol memories were retrieved not only by the stimuli of the operant setting associated with alcohol, but also by the intrinsic sensory properties of alcohol per se (i.e., odor-taste cues) given in the home cage. Barak et al. (2013) suggested that the latter retrieval method may evoke alcohol memories in a more general manner, as odor and taste are common characteristics of many experiences with alcohol and are generalizable beyond specific contexts and cues.

Rapamycin was also shown to disrupt the reconsolidation of alcohol memories formed in a place-conditioning paradigm (Lin et al. 2014). Specifically, the post-retrieval systemic administration of rapamycin (10 mg/kg) decreased the expression of alcohol-conditioned place preference (CPP). This effect was shown to last 14 days and was not reversed by a priming injection of alcohol (Lin et al. 2014).

2.2 β-Adrenergic Receptor Blockade

Early pharmacological interventions with memory reconsolidation involved the inhibition of β-adrenergic receptors (Roullet and Sara 1998; Przybyslawski et al. 1999; Milton et al. 2008). However, the effects of such treatment on alcohol memory reconsolidation remain somewhat inconclusive. In a mouse CPP paradigm, the β-adrenergic receptor blocker propranolol (10 or 30 mg/kg) did not affect the reconsolidation of alcohol-related memories when given after such memory retrieval (Font and Cunningham, 2012), despite being effective for other drugs of abuse (e.g., Fricks-Gleason and Marshall 2008; Robinson et al. 2011; Xue et al. 2017).

In a rat operant self-administration study, propranolol (2 μg per hemisphere) or vehicle was injected into the basolateral amygdala (BLA) following a training

session aimed at retrieving alcohol-related memories. When tested a day later, propranolol-treated rats showed reduced responses for alcohol in the first six trials. However, no difference between groups was found in the subsequent 12 trials, probably due to extinction in the control vehicle-treated group (Chesworth and Corbit 2018), thus limiting the conclusions of this study. In another operant self-administration study in rats, administration of propranolol (10 mg/kg) 30 min prior to the retrieval of alcohol-related memories had no effect on alcohol-seeking behavior (Milton et al. 2012). In a subsequent study, however, systemic β-adrenergic receptor blockade was shown to impair reconsolidation of certain aspects of alcohol-associated memories, namely, those involving second-order conditioning. In contrast, the adrenergic prodrug dipivefrin (10 μg/kg) enhanced such reconsolidation, suggesting that the reconsolidation of specific aspects of alcohol memories can be bidirectionally modulated by reducing or enhancing central adrenergic signaling (Schramm et al. 2016). In another study, a single post-retrieval injection of propranolol (10 mg/kg) following a memory-retrieval session did not affect the reconsolidation of alcohol memories. Moreover, repeated post-retrieval injections of propranolol had no effect on extinction (Williams and Harding 2014). It is also of note that alcohol-seeking behavior was reduced only when propranolol was given following memory retrieval in 2–3 sessions (Wouda et al. 2010), raising the possibility that the reconsolidation of alcohol memories can be impaired only by repeated administration of β-adrenergic blockers.

Unlike most protein synthesis inhibitors, which cannot be used on human subjects, propranolol is an FDA-approved drug for various clinical indications and can, therefore, potentially be used with human AUD patients. In a double-blind, small sample size study of hazardous drinkers, treatment-seeking adults diagnosed with substance dependence received double-blind propranolol or placebo in six bi-weekly sessions (over 3 weeks) prior to memory retrieval via exposure to drug-related visual cues and self-reported craving measurement (Lonergan et al. 2016). Propranolol given prior to alcohol memory retrieval was found to reduce self-reported craving intensity only by the sixth session (Lonergan et al. 2016).

Taken together, these mixed findings suggest that the efficacy of β-adrenergic receptor blockade for disrupting reactivated memories might depend on methodological parameters, such as the number of repeated retrieval-propranolol cycles. Moreover, since the adrenergic system plays a well-documented role in arousal and attention (Aston-Jones et al. 1999; Robbins 2000; De Martino et al. 2008; Thiele and Bellgrove 2018), it is possible that β-adrenergic receptor blockers alter the arousal associated with alcohol cues, thereby affecting the intensity of memory destabilization and reconsolidation.

2.3 NMDA Receptor Blockade

Another pharmacological manipulation widely used for disrupting memory reconsolidation is the blockade of NMDA receptors. Indeed, such manipulation

was shown to at least partly interfere with the reconsolidation of alcohol-associated memories in several studies. In an operant self-administration study, rats were trained to press a lever in response to olfactory and auditory cues paired to alcohol delivery. Following a period of abstinence, alcohol memories were activated via a short (5 min) re-exposure to the alcohol-associated cues and non-reinforced lever pressing. The NMDA receptor antagonist MK-801 (0.1 mg/kg), injected immediately following memory retrieval, reduced cue-induced increase in alcohol seeking, as compared to vehicle-treated controls. However, 7 days later, MK-801-treated rats only showed a non-significant trend toward reduced alcohol seeking (von der Goltz et al. 2009). This finding may indicate that the effects of NDMA receptor blockade might be temporary and decay with time, suggesting that cue-drug memory was not permanently affected, as expected from disruption of reconsolidation mechanisms. Moreover, in the same study, the FDA-approved drug acamprosate, a combined GABA receptor agonist/NMDA receptor antagonist used for alcohol use disorder treatment, failed to affect alcohol seeking when injected after alcohol memory retrieval (von der Goltz et al. 2009).

When given repeatedly after several sessions of memory retrieval, the effects of MK-801 on alcohol memory reconsolidation and seeking behavior were less conclusive. In one study, rats were first trained to nose poke for alcohol rewards in response to cues signaling alcohol availability and delivery. After an abstinence period of 3 weeks, memories were retrieved upon presentation of the alcohol-associated cues in a 20-min session, followed by MK-801 or saline injection. Alcohol seeking was tested 24 h later. The cycle of retrieval, MK-801 treatment and testing were repeated three times. Only in a trend toward reduction in alcohol seeking upon such treatment was observed (Wouda et al. 2010).

In a well-controlled study, injection of MK-801 30 min before (rather than after) alcohol memory retrieval was shown to disrupt the reconsolidation of alcohol memories and reduce alcohol seeking (Milton et al. 2012). In this study, the test was performed by comparing lever pressing in the presence of the alcohol-predicting versus non-predicting cues. Rats treated with MK-801 before memory retrieval showed similar degrees of lever pressing for both types of cues, whereas saline-treated controls increased lever pressing upon presentation of the alcohol-paired cues (Milton et al. 2012). However, when retrieving memory with a short non-reinforced lever-responding session rather than alcohol cues, alcohol seeking was found to be unaffected. The authors interpreted these findings as suggesting that operant memories are more resistant to NMDA receptor blockade following retrieval, as compared with Pavlovian cue-alcohol memories (Puaud et al. 2018). This suggestion is consistent with previous reports showing that targeting memories underlying operant behavior via reconsolidation mechanisms has been particularly challenging (Exton-McGuinness et al. 2019, 2014), although other manipulations were shown to be more effective in operant settings (Xue et al. 2012; Exton-McGuinness et al. 2014; Exton-McGuinness and Lee 2015; Luo et al. 2015; Goltseker et al. 2021).

Memantine, another NMDA receptor antagonist, was also shown to disrupt alcohol seeking in a rat operant self-administration procedure, but surprisingly reduced seeking behavior, regardless of memory retrieval (Vengeliene et al. 2015).

Rats receiving two memantine injections (20 mg/kg) or vehicle, given both shortly and 4 h following a memory retrieval (5 min training session), showed reductions in a cue-induced alcohol-seeking test conducted 24 h later, compared with vehicle-treated controls. However, rats that received memantine with no prior memory retrieval also showed reduced alcohol seeking. This finding suggests that memantine suppressed alcohol seeking 24 h after its administration, regardless of memory retrieval (Vengeliene et al. 2015), and emphasizes the importance of crucial control conditions in alcohol memory reconsolidation studies, namely, no treatment and no-retrieval controls.

NDMA receptor blockade was also considered in human hazardous drinkers, where the administration of ketamine following the retrieval of the alcohol-associated memories reduced the reinforcing effects of alcohol and long-term (up to 9 months) drinking levels, compared with ketamine given without retrieval or with retrieval with no ketamine administration (Das et al. 2019). Thus, targeting the NMDA receptor may have clinical benefits in reducing alcohol relapse, presumably by affecting reconsolidation mechanisms.

In summary, blocking NMDA receptors appears to be a promising strategy for disrupting alcohol memory reconsolidation, with current results seemingly more consistent than those from studies targeting the adrenergic system. Still, temporal and procedural parameters should be carefully chosen in future efforts to ensure successful and long-lasting effect. Moreover, a close examination of the available data reveals that manipulations in which NMDA receptors were blocked had more pronounced effects on newer rather than on older memories (Barak and Goltseker 2021).

3 Behavioral Interference with Alcohol Memory Reconsolidation

Pharmacological treatments given during memory reconsolidation may have side effects and may even be toxic (Tronson and Taylor 2013; Lee et al. 2017; Barak and Goltseker 2021). It has been shown in fear memory and drug memory studies that behavioral interventions given following memory retrieval (presumably during the reconsolidation window) can have stronger and longer effects of suppressed behavioral responses, as compared with behavioral interventions given without prior memory retrieval (Monfils et al. 2009; Ma et al. 2012; Xue et al. 2012; Hutton-Bedbrook and McNally 2013; Sartor and Aston-Jones 2014).

The most-studied behavioral intervention applied following retrieval is extinction training. While extinction inhibits the conditioned response, it does not prevent the return of the response that may occur due to the passage of time (spontaneous recovery) or upon re-exposure to the reinforcer (reinstatement) or to the learning context (renewal) (Barak and Ben Hamida 2012). However, it has been suggested that when extinction training is applied following memory retrieval, such training

prevents the return of the conditioned response, i.e., the previous memory is disrupted (Monfils et al. 2009; Xue et al. 2012; Hutton-Bedbrook and McNally 2013; Kuijer et al. 2020). Using this approach, Cofresi et al. (2017) showed that memory retrieval prior to extinction training reduced alcohol-seeking behavior, as compared with extinction with no memory retrieval. In this study, alcohol was paired with a visual cue. Over the following 14 sessions of extinction training in which the cue was presented without alcohol, the retrieval group received an hour-long time out in the home cage between the first two extinction trials, so as to retrieve alcohol memories and initiate their reconsolidation. In a test session, rats that underwent extinction training during memory reconsolidation then showed reduced spontaneous recovery and reinstatement of the conditioned response to alcohol-associated cues, suggesting that the retrieval-extinction procedure reduced relapse to alcohol seeking (Cofresi et al. 2017).

Using an elegant experimental design, it was demonstrated that extinction suppresses alcohol-seeking behavior both not only when given after memory retrieval, but also when given before a memory-retrieval session (Millan et al. 2013). In this study, rats self-administered decarbonated beer in one context (context A), whereas extinction training was conducted in a distinct context (B). Rats then received a 50-min extinction session, with an additional 10-min retrieval session given either 70 min before extinction (the retrieval-extinction group) or after extinction (the extinction-retrieval group). In a test conducted in the alcohol-associated context A, animals that underwent extinction before or after memory retrieval showed a reduced renewal effect (context-induced reinstatement) of alcohol-seeking behavior, compared with no-retrieval controls (Millan et al. 2013). Although the capacity of retrieval-extinction to reduce alcohol seeking can be interpreted as extinction occurring during the reconsolidation window, in turn leading to memory updating, the similar outcome of extinction-retrieval training cannot be interpreted in terms of reconsolidation. An alternative explanation is that retrieval + extinction sessions (regardless of their order) are more effective in reducing responding for alcohol, compared with a single extinction training (no-retrieval controls), despite the total extinction time being equal (60 min). Moreover, retrieval-extinction facilitated the reacquisition of alcohol self-administration, stressing the limitation of this procedure in reducing alcohol seeking. Together, these findings suggest that the retrieval-extinction approach has limited effectivity in disrupting the memory and seeking response (also see Luyten and Beckers 2017).

Another behavioral approach aimed at reducing alcohol and drug seeking via post-retrieval, reconsolidation mechanisms uses reassociation of the alcohol/drug-associated cues with an aversive outcome, i.e., application of aversive counterconditioning or punishment training following memory retrieval. In this approach, a cue or action that was previously paired with the reinforcing effects of alcohol is re-associated with aversive consequences (Cannon et al. 1981). Cue-aversion therapy, based on counterconditioning, showed stronger effects than extinction in reducing relapse in animal models and human studies (Van Gucht et al. 2010; Tunstall et al. 2012) and helped alcohol drinkers remain abstinent for longer periods (Elkins et al. 2017). These effects are, however, typically transient (Bouton and Peck

1992; Brooks et al. 1995; van Dis et al. 2019), and relapse can occur (Bouton and Peck 1992; Brooks et al. 1995).

Using a place-conditioning paradigm, Goltseker et al. (2017) showed that the application of aversive counterconditioning shortly after the retrieval of a context-cocaine memory prevented the expression of cocaine CPP in a prime-induced reinstatement test, considered to model the relapse to cocaine seeking (Goltseker et al. 2017). This effect was long-lasting (at least 35 days) and was seen only when counterconditioning followed memory retrieval. No effect was observed when the gap between retrieval and counterconditioning was 5 h. Moreover, counterconditioning prevented reinstatement of drug seeking only when applied after, but not before, memory retrieval (Goltseker et al. 2017). This is in contrast to the previous observation of the equivalent effects of retrieval-extinction and extinction-retrieval procedures on alcohol seeking (Millan et al. 2013), suggesting that the disruption of drug seeking is indeed mediated by memory reconsolidation mechanisms.

Using a similar approach, the same group demonstrated that a relapse to alcohol seeking could be prevented by aversive counterconditioning conducted during alcohol memory reconsolidation in both classical and operant learning paradigms (Goltseker et al. 2021). In this alcohol-CPP study, following establishment of CPP, the alcohol-associated context was counterconditioned with an aversive experience, specifically, a "flood" of cold water (Goltseker and Barak 2018), preceded by memory retrieval. Similar to the cocaine study described above, aversive counterconditioning conducted shortly following alcohol memory retrieval prevented the reinstatement of alcohol CPP, suggesting that aversive training had disrupted the retrieved alcohol memory (Goltseker et al. 2021). In fact, mice that underwent retrieval-counterconditioning manipulation avoided the alcohol-associated context during testing (Goltseker et al. 2021), suggesting that aversive information presented following memory retrieval can be incorporated into the originally-retrieved memory, thereby updating the information and perhaps even replacing the previous association (Das et al. 2015a; Goltseker et al. 2017; Lee et al. 2017; Gisquet-Verrier and Riccio 2018; Barak and Goltseker 2021; Goltseker et al. 2021). An interesting finding of the study was that retrieval followed by aversive counterconditioning was characterized by the upregulation of brain-derived neurotrophic factor (*Bdnf)* mRNA expression in the medial prefrontal cortex, suggesting that BDNF plays a role in the memory updating process (Goltseker et al. 2021).

The retrieval-counterconditioning paradigm was also adjusted to an operant self-administration procedure that models relapse-like alcohol-related behaviors (Burattini et al. 2006; Goltseker et al. 2019). Here, in an operant alcohol self-administration procedure, rats were trained to lever press for alcohol in context A for 2 months. Then, the alcohol memory was retrieved by exposing the rats to the odor-taste alcohol cue for 10 min in the home cages, whereas control rats received the same punishment training with no prior memory retrieval (Goltseker et al. 2021). As expected, the control (no-retrieval) group showed renewal of alcohol seeking (i.e., non-reinforced lever pressing) when returned to the alcohol-associated context A, modeling context-induced relapse to alcohol seeking (Goltseker et al. 2021). However, when alcohol memory retrieval was applied prior to the

punishment, the renewal of alcohol seeking was suppressed. In addition, when memory retrieval was given long before the punishment, the rats showed reinstatement, demonstrating the punishment to be effective in preventing relapse only when given during the reconsolidation window. Interestingly, this renewal effect, or context-induced reinstatement of seeking behavior, can model the high rates of relapse which are commonly observed in AUD patients, who even after successful treatment in the clinics experience strong cravings and relapse upon re-exposure to the environment in which they once consumed alcohol (Witteman et al. 2015).

In a laboratory-controlled experiment, the post-retrieval counterconditioning procedure was also shown to successfully update an appetitive memory with aversive information in humans (Gera et al. 2019). Moreover, this approach was also shown to be beneficial in modulating craving and drinking patterns in hazardous alcohol drinkers (Das et al. 2015a, 2018; Gale et al. 2020). In these studies, abstinent hazardous alcohol drinkers received alcohol memory retrieval by being presenting with a glass of beer and then taking it away unexpectedly before the first sip (Das et al. 2015a, 2018, 2019; Hon et al. 2016). Alcohol cues were then re-associated with gustatory and visual disgust (eight pairings for each modality) (Das et al. 2015a). The results showed subsequent reductions in alcohol cue valuation and alcohol craving (Das et al. 2015a). Furthermore, this procedure was reported to suppress drinking in a long-lasting manner (i.e., for 9 months) (Gale et al. 2020). Taken together, these findings suggest that similar to what has been reported in animal models, counterconditioning applied following alcohol memory retrieval in humans can lead to integration of the new information into the memory, by "rewriting" the valence of alcohol cues.

An additional strategy for targeting alcohol memory reconsolidation in hazardous drinkers in a non-pharmacological manner is reappraisal of maladaptive alcohol memories, which utilizes a cognitive psychotherapy given within the memory reconsolidation window (Hon et al. 2016). Another form of interference yielded unexpected results, whereby high working memory load reduced alcohol craving in heavy drinkers when given before memory retrieval, with no such effects being seen when given after retrieval (Kaag et al. 2018). Together, the few attempts to reduce alcohol craving and relapse by post-retrieval behavioral and/or cognitive manipulation point to therapeutic potential, however, further exploration and thorough characterization of this direction of therapy are still needed.

4 Summary and Conclusions

In this review, we surveyed studies that utilized two primary mechanisms shown to disrupt performance via interference with the memory reconsolidation process: a) disruption of alcohol memory reconsolidation via pharmacological manipulations that are thought to prevent the restabilization of the memories and b) updating, replacing, or incorporating new (typically conflicting) information into the original cue-alcohol memory, via behavioral and/or cognitive training conducted following

memory retrieval, i.e., during the "reconsolidation window," when memory is considered to be flexible (Fig. 1).

We have recently raised several critical remarks regarding the standardization of research and the replicability of results in the reconsolidation field in general, and specifically, in drug and alcohol memory reconsolidation studies (Barak and Goltseker 2021). Furthermore, we also raised concerns regarding the translational limitations of reconsolidation-based treatment strategies (Barak and Goltseker 2021). Below is a summary of the points most relevant for studies on alcohol memory reconsolidation.

4.1 Methodological Standardization and Inconsistent Findings

Most studies on memory reconsolidation in animal models have relied on classical fear conditioning memories (Nader and Hardt 2009; Lee et al. 2017). Even in this relatively standard and simple classical conditioning paradigm, inconsistent findings in fear-memory reconsolidation have been reported, presumably due to methodological variability (Barak and Ben Hamida 2012; Luyten et al. 2021; Schroyens et al. 2021). Studies on reconsolidation of drug- and alcohol-associated memories typically include even greater methodological variability, due to the diverse nature of these studies. Thus, addiction-like behaviors are modeled both in classical and operant learning paradigms, as detailed above, with various very different protocols that may reflect different aspects of addiction being used. Therefore, inconsistency in

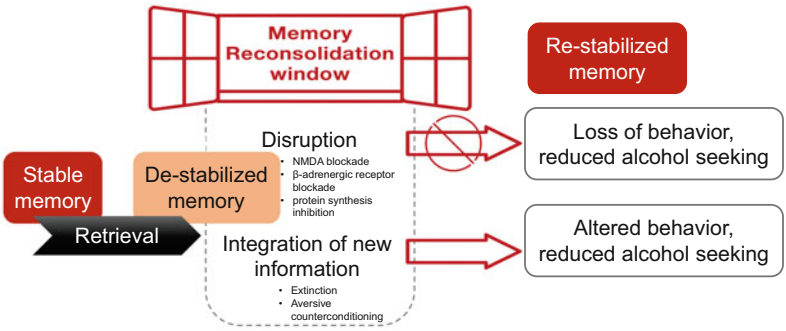

Fig. 1 Reducing alcohol seeking by post-retrieval manipulation – schematic illustration. According to the reconsolidation hypothesis, stable memories de-stabilize upon retrieval and undergo a time-dependent process of restabilization. Amnestic pharmacological treatment delivered shortly after memory retrieval (i.e., during the "reconsolidation window") can disrupt the restabilization process and prevent cue-induced craving and alcohol seeking (amnestic pharmacological agents). Alternatively, new information introduced following retrieval via behavioral manipulation (e.g., extinction or aversive counterconditioning) can be incorporated into the original memory, thereby preventing alcohol seeking, and even leading to avoidance of alcohol-related cues

findings with a given amnestic drug or behavioral intervention could be attributed not only to the limited efficacy of the treatment in disrupting the reconsolidation process, but also to the absence of standardized protocols with optimal experimental parameters.

Manipulations of alcohol and drug-associated memory reconsolidation were shown to be more effective in classical conditioning paradigms (e.g., CPP), as compared with drug-memories formed in operant paradigms (Barak and Goltseker 2021). For example, in an alcohol study that tested a similar post-retrieval treatment both in CPP and operant alcohol self-administration procedures, manipulation led to a complete abolition of drug seeking in CPP, but only to a partial decrease in seeking of the operant response (Goltseker et al. 2021). A similar pattern was observed with other drugs of abuse (e.g., Xue et al. 2012). Indeed, memories formed in operant procedures are thought to be less sensitive to memory reconsolidation manipulations, and it seems that effects are demonstrated only within a limited window of procedural parameters (Hernandez and Kelley 2004; Brown et al. 2008; Mierzejewski et al. 2009; Xue et al. 2012; Exton-McGuinness et al. 2014; Piva et al. 2020). It is important to bear in mind that while place-conditioning procedures may provide convenient models of alcohol/drug reward and seeking, they are not considered as models of addiction (Goltseker et al. 2019; Barak and Goltseker 2021). Rather, operant self-administration procedures model various aspects of addiction phenotypes with considerably higher validity. Thus, the limited and inconsistent findings of reconsolidation experiments conducted in operant settings are a critical limitation of this approach as a translational research field (see below).

Importantly, even when using the same conditioning paradigm (e.g., operant alcohol self-administration), the specific training protocols used by different research laboratories vary considerably. In particular, there are differences in the duration of training prior to manipulation, in the reinforcement schedules used for training and testing, in the doses of drugs administered, in withdrawal periods prior to memory retrieval (if any), in the memory-retrieval methodology itself, in the timing of manipulation (i.e., before/after memory retrieval), and in post-manipulation testing (under extinction conditions or not, number of tests sessions and more). Therefore, the absence of standardization in experimental design and procedure may largely account for the inconsistency in the findings in the field of alcohol and drug memory reconsolidation (Barak and Goltseker 2021). Relatedly, a publication bias, whereby negative results are not published, was suggested as affecting reconsolidation studies in other types of memories (Schroyens et al. 2021) and may also occur in the case of alcohol memory reconsolidation.

It is also important to bear in mind that negative results following post-retrieval manipulations can reflect the low effectivity of the manipulation in disrupting memory reconsolidation, but can also reflect non-successful reactivation of the memories via retrieval. To ensure that the retrieval procedures are validated in the experimental protocol, it would be beneficial to use treatments previously shown to potently disrupt memory reconsolidation in various experimental procedures (e.g., using protein synthesis inhibitors (Nader et al. 2000; Lee et al. 2017; Exton-McGuinness and Milton 2018; Taujanskaite et al. 2020; Barak and Goltseker 2021)).

A related methodological concern that can affect theoretical interpretation of the data comes from the fact that retrieval procedures are typically based on a short non-reinforced presentation of the cue in an extinction-like session. Disruption of memory reconsolidation and extinction training may yield similar effects, i.e., reduced performance in a retention test (Barak and Ben Hamida 2012; Barak and Goltseker 2021). However, following extinction, the conditioned response may return, presumably reflecting the ability of the previous memory trace to control behavior. Thus, testing the return of the extinguished behavior via spontaneous recovery, renewal and reinstatement tests can potentially distinguish between the effects of extinction and reconsolidation disruption, as the conditioned response is expected to return only in the former (Duvarci and Nader 2004; Barak and Ben Hamida 2012; Barak and Goltseker 2021).

Finally, manipulations that target the reconsolidation process should be applied shortly after memory retrieval (i.e., within the memory reconsolidation window), and not before memory retrieval, as the memory retrieval is thought to initiate the reconsolidation process. Nevertheless, in the case of pharmacological manipulation, pharmacokinetic and pharmacodynamic considerations might justify earlier administration of amnestic drugs. However, applying manipulations before memory retrieval can potentially affect memory retrieval itself, and not only the memory reconsolidation process, limiting the theoretical interpretation of the results.

4.2 Applicative and Clinical Limitations

Disruption of drug- and alcohol-associated memory reconsolidation has been proposed as a strategy to prevent cue-induced craving and relapse in substance use disorders (Milton 2013; Exton-McGuinness and Milton 2018; Monfils and Holmes 2018; Goltseker et al. 2019; Barak and Goltseker 2021). However, several limitations or "boundary conditions" on memory reconsolidation have been discussed in the literature (e.g., Dunbar and Taylor 2017; Treanor et al. 2017; Exton-McGuinness and Milton 2018; Monfils and Holmes 2018), which may substantially limit the translation of memory reconsolidation approaches into clinical applications.

Alcohol induces not only rewarding, but also aversive effects (Cappell et al. 1973), with extensive training being required to achieve high and stable levels of self-administration. For example, operant alcohol self-administration usually requires an initiation phase, in which rodents are exposed to alcohol in the home cage in 2-bottle choice procedures for several weeks before starting operant training that continues for several additional weeks. Therefore, rodents are typically trained to drink alcohol for 1.5–3 months prior to testing (Carnicella et al. 2014). Such extensive training, which is parallel to the extensive exposure to alcohol seen in human AUD patients, affects two of the boundary conditions suggested to blunt the susceptibility of memory reconsolidation for disruptive manipulations, namely, the age of the cue-alcohol memory and its strength. Importantly, AUD patients always have a long and intensive history of alcohol consumption. Hence, their alcohol-

associated memories are old and strong, making this methodological necessity a translational advantage. However, as suggested in the literature (Dunbar and Taylor 2017; Treanor et al. 2017; Exton-McGuinness and Milton 2018; Monfils and Holmes 2018), self-administration memories in animal models, as the strong and intensive memories in AUD patients, become less susceptible to changes and to reconsolidation manipulation. Nevertheless, when effects on alcohol memory reconsolidation are demonstrated despite the extensive training obstacle, the effects likely have greater translational validity.

In addition, in experiments conducted in the laboratory, the retrieval of a specific cue-alcohol memory via a short presentation of the cue allows targeting of specific memories in a relatively precise manner. In contrast, clinical situations are obviously not as "sterile." Patients treated in the clinic already have well-consolidated and intensive alcohol-associated memories in which the reinforcing effects of alcohol are associated with multiple contexts and stimuli, leading to heavily habitual and even compulsive responses. Therefore, in the clinical setting, memories comprise complex networks of multiple stimuli and responses and reinforcements that are all interconnected (Barak and Goltseker 2021). Thus, targeting an isolated "cue-alcohol" memory trace is likely to yield very limited clinical outcomes. Indeed, translation of laboratory findings of reconsolidation studies to clinical settings has encountered difficulties (Das et al. 2015b; Jobes et al. 2015; Treanor et al. 2017). A potential solution for this challenge would be to retrieve the memory using odor-taste cues (Barak et al. 2013; Goltseker et al. 2021). Since the odor and taste of alcohol are an intrinsic characteristic of any experience with this substance, they are expected to prompt reactivation of multiple memories associated with the alcohol, allowing their simultaneous targeting.

Finally, the drug-taking context typically differs greatly from the context of clinical treatment. This gap may cause renewal of the conditioned response, leading to "context-induced relapse" whereby patients return of their natural environment upon completion of clinical therapy. This clinical issue can be modeled in the laboratory by renewal experiments in which the acquisition of alcohol self-administration is conducted in one context (context A) and the treatment (e.g., extinction, counterconditioning, punishment) is given in another context (context B). To demonstrate renewal and relapse-like behavior, the animals are subsequently tested in the alcohol-associated context A again, leading to the return of the previous behavior acquired in context A (ABA renewal design) (Bouton 2002; Marchant and Kaganovsky 2015; Marchant et al. 2018, 2019; Goltseker et al. 2021). Recently, we reported that application of a punishment following alcohol memory retrieval in an ABA-experimental design attenuated the context-induced relapse-like effect in operant self-administration model in rats, suggesting that using memory retrieval and reconsolidation mechanisms might allow for overcoming the context-dependency issue (Goltseker et al. 2021).

The concept of memory reconsolidation and the theoretical interpretation of results in this framework have been controversial, and alternative theoretical interpretation has been suggested (e.g., Gisquet-Verrier and Riccio 2018; Kiley and Parks 2021). Thus, as amnestic pharmacological treatments modify the internal state of the

subject, it has been suggested that new information can be associated or encoded with the post-retrieval active memory and become a part of it, thus causing state-dependency (Gisquet-Verrier and Riccio 2018). According to this hypothesis, the internal state induced by treatments such as propranolol, MK-801, or rapamycin is integrated into the contextual cue-alcohol memory, which could be retrieved after such integration only in this specific internal state. This hypothesis, therefore, provides a testable prediction, namely, that the conditioned response (alcohol seeking) will be restored following infusion of these "amnestic" drugs (Gisquet-Verrier and Riccio 2018; Kiley and Parks 2021). Nevertheless, the finding that alcohol seeking can be disrupted by post-retrieval manipulation is still valid in both interpretations.

In summary, in this review we surveyed evidence for the potential of reconsolidation disruption and aversive counterconditioning manipulation in attenuating alcohol relapse. However, the inconsistency of findings in the field, along with the methodological and conceptual weaknesses discussed above, may limit the replicability and potential translational value of these findings. Therefore, there is a clear need for more systematic, well-controlled, and standardized research that will address these critical issues in future.

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