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Can Memories of Traumatic Experiences or Addiction Be Erased or Modified? A Critical Review of Research on the Disruption of Memory Reconsolidation and Its Applications

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Abstract
Recent research suggests that the mere act of retrieving a memory can temporarily make that memory vulnerable to disruption. This process of "reconsolidation" will typically restabilize the neural representation of the memory and foster its long-term storage. However, the process of reconsolidating the memory takes time to complete, and during this limited time window, the original memory may be modified either by the presentation of new information or with pharmacological agents. Such findings have prompted rising interest in using disruption during reconsolidation as a clinical intervention for anxiety, posttraumatic stress, and substance use disorders. However, "boundary conditions" on memory reconsolidation may pose significant obstacles to clinical translation. The aim of this article is to critically examine the nature of these boundary conditions, their neurobiological substrates, and the potential effect they may have on disruption of reconsolidation as a clinical intervention. These boundary conditions also highlight potential constraints on the reconsolidation phenomenon and suggest a limited role for memory updating consistent with evolutionary accounts of associative learning for threat and reward. We conclude with suggestions for future research needed to elucidate the precise conditions under which reconsolidation disruption may be clinically useful.

Keywords
memory reconsolidation, posttraumatic stress, substance use, translational research

Although much of the lay public holds the belief that memories are permanent and cannot be edited or erased (Simons & Chabris, 2011), psychological and neuroscientific research has long suggested otherwise (e.g., Bartlett, 1932). A growing body of evidence indicates that memories can be altered, sometimes profoundly, when they are recalled. Under certain conditions, retrieval of a memory can return the original memory trace to a labile state in which new information can be woven into the memory and old information can be weakened or lost. For example, following repeated pairings of a tone with an electric shock, an animal will learn to fear the tone. If the tone is later presented without a shock, it will likely remind the animal of the aversive shock and transiently return the memory of the tone-shock association to a labile state. While in this vulnerable state, the fear association may be "erased" with administration of certain pharmacological agents or behavioral interventions. Several studies in animal and human samples have demonstrated such modification of a memory, and behaviors associated with that memory, through the process termed *memory reconsolidation* (Nader, Schafe, & LeDoux, 2000; see Appendix).

These basic research findings have prompted a great deal of excitement in both the scientific community and in the larger media. For example, news headlines such as "A Drug to Cure Fear" (Friedman, 2016) and "New Drug Deletes Bad Memories" (Christensen, 2007) are common,

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and researchers continue to note the potential therapeutic efficacy of disrupting reconsolidation for disorders such as posttraumatic stress disorder (PTSD) and substance abuse (Lane, Ryan, Nadel, & Greenberg, 2015; Milton, 2013; Parsons & Ressler, 2013; Pitman, 2011; Schwabe, Nader, & Pruessner, 2014). Indeed, there have been some promising initial attempts at clinical translation (Lonergan et al., 2016; Soeter & Kindt, 2015; Xue et al., 2012), whereas others have failed to find any benefit of disruption in reconsolidation (Wood et al., 2015).

Anxiety disorders, PTSD, and substance use disorders are characterized by maladaptive memory processes. Pavlovian learning, in which a neutral stimulus (*conditional stimulus* or CS; see Appendix) comes to elicit behavior because it predicts the occurrence of a biologically significant stimulus (*unconditional stimulus* or US; see Appendix), is central to the genesis and maintenance of anxiety disorders, PTSD, and substance-use disorders (Lissek et al., 2005; Lissek et al., 2009; Milton, 2013; Mineka & Zinbarg, 2006). For example, following a traumatic experience such as a sexual assault, an individual may display fear and avoidance of stimuli that resemble the original CS (e.g., men of a certain age) or context where the assault occurred (e.g., dark rooms). In substance abuse, drug related paraphernalia or contexts in which drug use occurred might increase craving and drug-seeking behavior (Milton, 2013).

Given that these disorders are characterized by pathological memories, the ability to disrupt or erase these memories would offer a significant advance in treatment (Merlo, Milton, & Everitt, 2015). Current treatment approaches, such as exposure therapy, adopt a strategy based on extinction learning (see Appendix). Unfortunately, extinction learning is context-dependent, and individuals often experience a return of symptoms (e.g., fear or drug craving) upon reencountering the stimulus in a new environmental context that differs from extinction training (Bouton, 2004). This fragility of extinction may be one factor that contributes to a return of symptoms in some individuals following exposure therapy for anxiety disorders (Ginsburg et al., 2014) and to the limited efficacy of cue-exposure therapy (i.e., exposure to substance-related cues) for substance use disorders (Conklin & Tiffany, 2002). Consequently, alternative methods for treating anxiety, posttraumatic stress, and substance use disorders, such as disruption of reconsolidation, are an important research endeavor. Researchers have theorized that disrupting the reconsolidation of the original memory trace may allow one to effectively "erase" the fear memory (Agren et al., 2012; Schiller et al., 2009). Similarly, disrupting reconsolidation of drug or appetitive memories may "erase" the reward-based memory (Dennis & Perrotti, 2015; Milton, 2013).

Despite the promising basic research findings regarding disruption in reconsolidation, numerous laboratories have failed to replicate this phenomenon despite using similar methodology. These failures have led to the identification of limitations on the ability to destabilize and disrupt a memory (Lee, 2009). Limiting "boundary conditions" include the duration of the reminder trial, the age and strength of the memory, and the similarity between the environmental context in which the memory was initially acquired and that in which it is being retrieved (Chan, Leung, Westbrook, & McNally, 2010; Monfils, Cowansage, Klann, & LeDoux, 2009; Pedreira & Maldonado, 2003; Suzuki et al., 2004). Further boundary conditions proposed herein include the specificity of reminder cues (i.e., how perceptually similar does a reminder stimulus have to be to an element of the original memory?).

Unfortunately, such boundary conditions pose significant obstacles to the translation of reconsolidation processes to clinical interventions. The aim of this article is to critically examine the nature of these boundary conditions, their neurobiological substrates, and the potential effect they may have on disruption of reconsolidation as a clinical intervention for PTSD, anxiety, and substance use disorders. These boundary conditions also highlight constraints on the reconsolidation phenomenon and suggest a limited role for memory updating consistent with evolutionary accounts of associative learning for threat and reward. We conclude with suggestions for future research to elucidate the precise conditions under which disruption in reconsolidation may be clinically useful.

Reconsolidation: Phases and Difference From Extinction Learning

If we want to understand and appreciate the challenges of applying in clinical settings the disruption of reconsolidation techniques, we must first understand the various phases of the reconsolidation process and how these differ from those of traditional extinction learning. For a memory to undergo reconsolidation, it must first be retrieved, which is usually initiated via a brief "reminder trial" (see Appendix). As described above, after repeated pairings of a tone and shock, presentation of the tone alone may retrieve the memory of the shock. However, memory retrieval is not sufficient to initiate reconsolidation, as the memory must also become "labile" or "destabilized" and thereby susceptible to modification or disruption. Once a memory becomes labile it requires molecular processes, such as protein synthesis, in order to reconsolidate, and it is at this point that behavioral and pharmacological methods may disrupt or modify reconsolidation of the target memory (Tronson & Taylor, 2007).

Thus, reconsolidation describes the process by which a previous stored memory is activated, destabilized, and once again stabilized. Evidence for reconsolidation and memory lability comes from deficits in memory when this process is disrupted, often via selective targeting of molecular processes thought to subserve memory stabilization (e.g., protein synthesis; Nader & Hardt, 2009; Tronson & Taylor, 2007).

Extinction, on the other hand, involves the formation of a new memory trace. For example, following pairings of the tone and shock described above, the tone is repeatedly presented without the shock. This training may lead to the formation of a new memory trace ("tone does not equal shock"). Whether or not presentation of the tone alone results in extinction learning or reconsolidation depends on various boundary conditions (discussed later in this article) and whether the original memory becomes labile (reconsolidation) or a new memory trace is formed (extinction). In other words, reconsolidation purports to modify the original memory trace, whereas in extinction a separate memory trace is created, and the original memory trace remains (tone equals shock). The long-term efficacy of extinction is contingent upon retrieving and generalizing the extinction memory to new contexts and stimuli while inhibiting the original memory (Craske et al., 2008, 2012; Vervliet, Craske, & Hermans, 2013). The potential benefit of disrupting reconsolidation as a clinical intervention is that it can modify the original memory trace and therefore avoid the pitfalls of leaving the original memory trace intact—namely, return of symptoms. However, as described below, this is contingent upon the ability to return the original memory trace to a labile state and to disrupt reconsolidation.

Given that reconsolidation can target the original memory trace, it may provide the opportunity to effectively "erase" an association that previously elicited fear (e.g., traumatic memories) or craving (drug related associations). Researchers have frequently employed the term "erase" when describing the impact of disruptions in reconsolidation on memory processes (Agren et al., 2012; Schiller et al., 2009). This is not technically correct, as declarative knowledge about the past event remains, whereas emotional expressions (e.g., fear or craving) are mitigated. For example, in several studies in humans, individuals with experimentally disrupted reconsolidation were still aware that certain stimuli had been paired with shock, but they were significantly less afraid and physiologically aroused by these stimuli (Soeter & Kindt, 2011). This distinction is important, as the extent to which disrupting reconsolidation is specific to certain response symptoms, or represents permanent loss of fear or craving, is central to claims that it can be used effectively in clinical applications. We discuss this issue later in this article.

Boundary Conditions

Duration of reminder trial and trace dominance

In laboratory investigations of reconsolidation, training first associates a neutral stimulus (CS) with a particular outcome (a shock or drug administration). Following initial consolidation of the memory, the memory can once again become labile via a brief reminder trial. The reminder typically involves the presentation of the CS alone without its associated outcome. Studies suggest that this reminder trial must be of a specific duration; if the reminder is too short, reconsolidation is not initiated, whereas if the reminder is too long, extinction learning rather than reconsolidation can be engaged (Pedreira & Maldonado, 2003). Given that reconsolidation requires a brief reminder trial and that a very different process of extinction will be instantiated with longer reminder trials, precise control of the duration of the reminder is crucial for translating reconsolidation into clinical interventions. This translation may be difficult for numerous reasons.

First, the optimal duration of a reminder trial may depend on the timing during initial learning. In an elegant series of studies, rats were shocked after either 1 or 5 min in a specific context (i.e., context conditioning), and they received a reminder trial 72 hr later followed by either midazolam (known to disrupt reconsolidation) or saline (Alfei, Monti, Molina, Bueno, & Urcelay, 2015). The authors parametrically varied the length of the reminder trial (e.g., 30 s, 2 min, 6 min, 15 min) in order to determine the effect on reconsolidation and extinction. Reminder trials shorter than those used during acquisition (i.e., 30 s for the 1-min conditioning group, or 2 min for the 5-min conditioning group) failed to induce memory destabilization and subsequent disruption in reconsolidation, whereas reminder trials that exceeded the duration used during acquisition (2 min for the 1-min conditioning group and 6 min for the 5-min group) were sufficient to induce reconsolidation. Simply exceeding the duration of the initial context conditioning was not always sufficient, as animals in the 1-min conditioning group neither demonstrated disruption in reconsolidation nor extinction when reminded with a 6-min trial. However, when the reminder trial length greatly exceeded the conditions present during initial training (e.g., 15 min reminder trial for the 1-min conditioning group) extinction was initiated (Alfei et al., 2015). The importance of this study is that it extends previous results regarding the duration of the reminder trial (Pedreira & Maldonado, 2003; Piñeyro, Monti, Alfei, Bueno, & Urcelay, 2014) to include the temporal parameters of initial learning. Thus, it appears that it is not the absolute duration of the reminder trial that is

important for inducing reconsolidation, but rather its relationship to the duration of CS exposure during the initial conditioning. Should such effects hold up across species, this could present a considerable obstacle to the translation of reconsolidation into clinical interventions, as it may be may be impossible to determine the duration of the original conditioning at the time of the clinical treatment and therefore difficult to calibrate the optimal timing of the reminder trial.

Second, the tendency of individuals with PTSD, anxiety, or substance use disorders to mentally retrieve the CS (e.g., worry in anxiety disorders, craving in addiction) may interfere with the clinician's control over CS duration. The extant literature suggests that even mental retrieval of original learning may be sufficient to induce memory lability. For example, Hupbach, Gomez, Hardt, and Nadel (2007) asked participants to memorize a set of objects placed in a distinctive basket. Forty-eight hr later, participants engaged in a "reminder trial," in which they were asked to remember and describe some details about the original learning experience without recalling the specific objects. This self-generated reminder was sufficient to induce memory lability enabling reconsolidation of the original learning (although see Sederberg, Gershman, Polyn, & Norman, 2011, for an alternative interpretation of these results). Similar results have been obtained in extinction learning, as mentally reinstating the exposure context (i.e., vividly imagining a prior exposure therapy session as a clinical proxy of extinction) was sufficient to retrieve extinction/exposure learning and results in by decreased fear when an individual is tested in a new context (Mystkowski, Craske, Echiverri, & Labus, 2006). In a clinical setting, a patient receiving treatment is likely to be informed in advance that a treatment session may involve confrontation with a CS (e.g., a feared stimulus or drug paraphernalia). This individual may anticipate or mentally retrieve the CS for hours prior to treatment, thus inadvertently extending the duration of the CS reminder trial and potentially rendering any attempt at a brief reminder trial moot.

Third, even when taking into account the length of the CS during conditioning, the optimal duration or number of reminder trials may differ across the various classes of associative memories (threat, appetitive, Pavlovian, instrumental, etc.) within which disruption of reconsolidation is being assessed. In Pavlovian fear conditioning paradigms in humans and rodents, the single reminder trial necessary for memory reconsolidation typically lasts several seconds to a few minutes (e.g., 8 s to 3 min; Soeter & Kindt, 2011; Suzuki et al., 2004). However, in inhibitory avoidance paradigms (see Appendix), extinction (rather than reconsolidation) is initiated when the duration of the single reminder trial approaches a few minutes (200 s; Power, Berlau, McGaugh, & Steward, 2006). In appetitive conditioning protocols (see Appendix), multiple reminder trials (e.g., 10 to 18) are required in order to induce memory lability (Flavell & Lee, 2013; Milton, Lee, & Everitt, 2008); the same number of reminder trials would initiate extinction, rather than reconsolidation, in fear conditioning (Kindt & Soeter, 2013). Pavlovian, instrumental, and inhibitory avoidance memory associations are all likely to contribute to PTSD, anxiety, and substance use disorders (Milton, 2013). Unfortunately, the literature offers no clear guidelines regarding the reminder structure necessary to induce memory lability when multiple memory associations are involved.

Although the induction of extinction rather than reconsolidation through lengthy reminder trials might not be clinically detrimental, accurately controlling the CS duration is important when reconsolidation is combined with pharmacological agents. A substantial amount of research suggests that extinction learning is also subject to disruption in consolidation. For example, infusions of anisomycin (a protein synthesis inhibitor) into the hippocampus (a neurological structure critical for memory) disrupted reconsolidation of an avoidance memory in rodents when using a brief reminder trial (less than 5 s) but impaired extinction with a relatively longer reminder trial (200 s; Power et al., 2006). As extinction memories are more dominant with longer reminder trials, these findings have been interpreted within a so-called *trace dominance framework*. That is, whichever memory trace happens to be dominant at the time of retrieval will be susceptible to disruption of consolidation or reconsolidation (Eisenberg, Kobilo, Berman, & Dudai, 2003). Thus, with lengthy CS reminders leading to extinction learning, the administration of anisomycin would disrupt consolidation of extinction rather than the original memory trace, leaving fear or craving intact (Power et al., 2006).

Finally, several studies that examined extinction within the reconsolidation window (i.e., the period of time in which a memory is susceptible to disruption following retrieval) have found disruption in reconsolidation whether the reminder trial is administered before or after extinction training (Baker, McNally, & Richardson, 2013; Millan, Milligan-Saville, & McNally, 2013). Such findings raise significant questions regarding the mechanisms of certain amnestic treatments, as it is difficult to reconcile how reconsolidation can be initiated when the reminder trial follows, rather than precedes, extinction learning.

In sum, failure to control the duration or number of CS trials can have deleterious consequences. Extending the duration or number of reminder trials can inadvertently induce extinction rather than reconsolidation. Although extinction may not be detrimental clinically, it fails to target the intended mechanism of reconsolidation. In addition, extinction learning is context-dependent and susceptible to renewal (e.g., return of fear, increase in

cravings). In order for clinical treatment protocols to exploit the mechanisms of reconsolidation and its proneness to disruption, researchers must first be able to reliably predict the conditions under which reminder cues will trigger extinction versus reconsolidation. These two processes may be mutually exclusive, such that induction of extinction learning can prevent labilization and reconsolidation from occurring (Merlo, Milton, Goozée, Theobald, & Everitt, 2014). Inadvertently inducing extinction can also be detrimental when combined with protein synthesis inhibitors, as they would lead to failure to consolidate extinction learning (Power et al., 2006).

Unfortunately, the extant literature offers no clear guidelines on the specific CS duration or number of trials necessary to induce memory lability in humans, let alone within different types of memory associations (such as Pavlovian fear vs. appetitive or instrumental) that are all characteristic of clinical disorders. This presents several obstacles to clinical translation. For example, an individual seeking treatment for PTSD may be exposed to a CS either in real life or imaginally during treatment. Without clear guidelines, confrontation with a given CS may extend beyond the duration necessary to induce labilization and inadvertently trigger extinction. The appropriate length of the reminder trial may depend upon factors during initial learning (Alfei et al., 2015), although this may be difficult to determine retrospectively. In addition, repeated trials can increase the likelihood of extinction rather than reconsolidation. This may be compounded by tendencies to repeatedly mentally retrieve and rehearse the CS (Davey & Matchett, 1994). If a lengthy reminder trial (leading to extinction) is combined with pharmacological agents, then this may disrupt the consolidation of extinction learning and lead to the preservation, rather than the reduction, of fear. Further research is needed to more precisely explore the transition between the time-limited window of memory lability and the onset of extinction learning in humans. However, without clear guideline as to the necessary length and number of trials needed to induce reconsolidation, it may prove difficult to translate disruptions in reconsolidation into clinical interventions. This mirrors related research on the pharmacological enhancement of extinction learning (Smits et al., 2013), which suggests timing is crucial in determining the efficacy of an intervention.

Cue specificity

The majority of studies examining the disruption of reconsolidation use the same CS for initial training and memory reactivation. For example, a picture of a spider may be repeatedly paired with a shock during conditioning, and the same picture will later be used for the reminder trial (Soeter & Kindt, 2011). Although this approach may offer precise experimental control in a laboratory experiment, it is nearly impossible to reproduce the original CS in a clinical setting when treating patients with PTSD or substance use disorders. From the few studies that have evaluated the role of cue specificity in reconsolidation, evidence suggests that conditional stimuli not directly associated with the US do not induce memory lability, and disruptions in reconsolidation may not generalize to other conditional stimuli. For example, in a typical second order conditioning protocol, a neutral stimulus (e.g., CS1; light) is repeatedly paired with a shock. Once the individual or animal learns to fear the light, a second stimulus (e.g., CS2; tone) is repeatedly paired with the light in the absence of the shock. The individual will then become fearful of CS2 as it is predictive of CS1, which in turn is predictive of shock. To draw an analogy with PTSD, a verbal argument (CS2) might predict an angry partner (CS1), which is predictive of domestic violence. Rodents receiving second order conditioning (CS2 $\rightarrow$ CS1 $\rightarrow$ US) failed to show any disruption in reconsolidation to the CS1 when reminded with the CS2, despite the fact that these stimuli exist in an associative network (Debiec, Doyere, Nader, & LeDoux, 2006). It is important to note that the authors used infusions of anisomycin into the lateral and basal nuclei of the amygdala, which has been shown to disrupt reconsolidation in several other paradigms (e.g., Nader et al., 2000). Thus, even well-validated methods for disrupting reconsolidation were ineffective when a second order CS, rather than the original CS, is presented during the reminder trial.

In addition, when two CSs are conditioned separately (e.g., both tone and light are separately paired with a shock), disrupting the reconsolidation of one CS does not alter responding to the other. This has been demonstrated via both behavioral (Schiller et al., 2009) and pharmacological disruptions of reconsolidation (Doyére, Debiec, Monfils, Schafe, & LeDoux, 2007; Soeter & Kindt, 2011). The selectivity of reconsolidation appears to be partly mediated by the neural encoding of stimulus features in the amygdala, and it suggests that conditions during initial training may dictate whether the two CSs are encoded as separate entities or whether they are bound together in memory as a "compound stimulus"; reconsolidation is more likely when the stimuli are encoded as a compound CS (Debiec, Diaz-Mataix, Bush, Doyere, & LeDoux, 2013).

A few studies have examined disruption in reconsolidation to a compound stimulus when presenting one element of the compound during retrieval. Debiec and colleagues (2013) conditioned rats to a tone-light compound. Rats were then administered anisomycin following presentation of the tone element and tested to both the tone and the light 24 hr later. Rats treated with

anisomycin demonstrated decreased responding to the tone and the light compared to those treated with placebo, although disruption in reconsolidation was contingent upon presenting original elements of the compound CS (see below). However, when the two elements were conditioned separately rather than as a compound, disruption in reconsolidation was specific to the reminder stimulus. Specificity of disruption of reconsolidation to the original CS poses barriers to clinical translation. For example, treatment for anxiety and traumatic stress disorders most often entails exposure to generalization stimuli (stimuli that resemble but are not identical to the original CS) rather than the original CS. That is, exposure therapy for social anxiety may include social interactions that do not exactly replicate the social interactions in which an initial social rejection took place, and exposure therapy for claustrophobia is unlikely to involve exposure to the exact claustrophobic situation in which fear was first acquired years earlier. Similarly, exposure to drug paraphernalia in a treatment setting may not replicate the exact paraphernalia used during drug administration.

No studies to our knowledge have examined reconsolidation using generalization stimuli during the reminder trial. However, the extant literature regarding the neurobiology of stimulus generalization suggests that additional brain structures, beyond those implicated in reconsolidation and retrieval, may be engaged when using generalization stimuli (Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011; Xu & Südhof, 2013). Thus, generalization stimuli may not activate neural structures essential for memory reconsolidation. Additional evidence comes from the literature showing that extinction with a generalization stimulus does not generalize to the original CS (e.g., fear or craving remains intact; Vervliet, Vansteenwegen, Baeyens, Hermans, & Eelen, 2005). Insofar as extinction learning consists partly of modification of the associative strength of the CS (Myers & Davis, 2007), the failure of a generalization stimulus to change the associative strength of the original CS suggests that the generalization stimulus may not activate the original memory trace.

The stimulus selectivity of disruption in reconsolidation has important implications for the treatment of PTSD, anxiety, and substance use disorders given that associative networks are often composed of multiple, complex CSs. For example, a sexual assault survivor may be fearful of people resembling the perpetrator, physical intimacy, social situations, and the memory of the trauma itself. Yet none of these stimuli include the original conditional stimuli, and the associative network is likely composed of multiple conditional stimuli and second order stimuli. However, the research reviewed above suggests that the presentation of second order CSs or additional CSs during a reminder trial is unlikely to disrupt the original memory trace, and the extant literature on generalization stimuli suggests that they may be insufficient to retrieve the original trace. In addition, it is sometimes difficult to determine the precise nature of the original CS. For an individual with heroin addiction, is the original CS the needle or drug paraphernalia most often used by the individual? How closely must the reminder stimulus resemble the original CS to trigger memory labilization? Specificity in the stimuli required to elicit reconsolidation would be a considerable obstacle in the clinical translation of reconsolidation research given that treatment often entails use of generalization stimuli or requires exposure to multiple stimuli within an associative network. Further research using generalization stimuli and associated CSs during a reminder trial is needed to elucidate the exact parameters of stimulus specificity as a potential boundary condition.

Memory strength

The resistance to interference for more strongly established memories (e.g., those that have undergone more extensive training) has been well-established in the literature on kinetic and visuomotor tasks (see Krakauer, Ghez, & Ghilardi, 2005, for an example). Under many (albeit not all) conditions, stronger memories are also less susceptible to reconsolidation than are weaker memories (Suzuki et al., 2004). PTSD, anxiety, and substance use disorders are characterized by strong memories, thus potentially reducing the clinical utility of this intervention.

However, several studies have revealed that stronger memories can undergo reconsolidation under some conditions. Tests of conditioned place preference (CPP; see Appendix) in rats have demonstrated that although more strongly conditioned memories (i.e., those that have undergone more extensive training) are less susceptible to disruption of reconsolidation, a combination of more reminder trials with an amnestic agent (propranolol or midazolam) and a longer delay between training and reactivation can render strongly acquired memories susceptible to disruption (Robinson & Franklin, 2010). In addition, increasing the length of the reminder trial has been shown to induce memory lability for stronger memories (Suzuki et al., 2004), although, as mentioned previously, without clear guidelines as to the necessary CS duration to destabilize a memory, a lengthy trial can trigger extinction rather than reconsolidation.

An additional difficulty lies in the definition of "memory strength." Most studies use number of CS–US pairings as an indicator of memory strength. However, dominant models of associative learning suggest that as the CS becomes a reliable predictor of the US, there is less net associative change per trial (Rescorla & Wagner, 1972). In other words, learning proceeds more slowly with

repeated CS–US pairings. As more learning occurs early on in training and decreases as training proceeds, the relative difference between a few training trials and many repeated training trials may not be as great as is presumed. Thus, the definition used in many studies (i.e., number of trial pairings) may not be the best characterization of memory strength. Memory strength can also be affected by the intensity of the US. A more intense US elicits greater learning (Rescorla & Wagner, 1972). Indeed, some evidence suggests that increasing the strength of the US prevents disruption in reconsolidation (Kwak, Choi, Bakes, Lee, & Kaang, 2012). Thus, additional studies are needed where memory strength is manipulated in several ways prior to determining the impact of memory strength on reconsolidation.

In sum, the degree to which memory strength impacts reconsolidation may depend on a variety of factors. Although increasing the length or number of reminder trials may be sufficient to induce memory lability, extinction may be inadvertently triggered in some instances. The possibility that stronger memories are less susceptible to disruption of reconsolidation has a number of very important clinical implications. In the case of PTSD, for instance, additional traumatic experiences are common (Risser, Hetzel-Riggin, Thomsen, & McCanne, 2006). Similarly, those with social anxiety disorder may experience rejection more readily than those without social anxiety (Downey, Mougios, Ayduk, London, & Shoda, 2004). Therefore, at least some individuals with anxiety and PTSD are likely to experience repeated aversive events that strengthen their threat-based memories, whereas individuals with substance use disorders are likely to experience repeated paraphernalia–drug pairings that may strengthen these associations. In addition, repeated mental rehearsal of the original memory (e.g., through worry or craving) may strengthen the underlying memory and pose an obstacle to reconsolidation disruption. Indeed, repeated labilization and reconsolidation of a declarative memory limits the impact of behavioral strategies designed to disrupt reconsolidation (Forcato, Fernandez, & Pedreira, 2013). This is further compounded by the fact that memory strength may also interact with the age of the memory (see below) to determine susceptibility to reconsolidation (Wang, de Oliveira Alvares, & Nader, 2009). However, more neurobiological research is needed to understand the underpinnings of reconsolidation, and the conditions under which strong and weak memories differ in their susceptibility to this phenomenon.

Age of the memory

Disruption of reconsolidation is time-dependent and may be more difficult with older memories, although findings regarding the age of memories are not entirely consistent. Protein synthesis inhibitors do not disrupt reconsolidation in rats when reminder trials are conducted 2 to 4 weeks following initial fear acquisition, but they do disrupt reconsolidation when reminder trials are conducted 2 to 8 days after training (Inda, Muravieva, & Alberini, 2011; Milekic & Alberini, 2002). Similar effects are found across species. In mice, anisomycin disrupts reconsolidation when reminder trials are given 1 day after training but not when they are given 36 days after training (Frankland et al., 2006). Another pharmacological agent, hemicholinium, an inhibitor of the high-affinity choline uptake in the brain, also disrupts reconsolidation in mice. Disruption of reconsolidation occurs 2 to 7 days after training if hemicholinium is administered following the reminder trial (Boccia, Blake, Acosta, & Baratti, 2006). However, no disruption occurs if a reminder trial plus hemicholinium occurs 14 or 30 days after training (Boccia et al., 2006).

Some research suggests that remote memories can become susceptible to disruption in reconsolidation with stronger reminder trials. Recent fear memories in mice acquired 1 to 3 weeks prior were susceptible to disruption in reconsolidation with anisomycin administered before a brief (3 min) reminder trial. Remote memories acquired 8 weeks prior were only susceptible to disruption in reconsolidation if given a longer (10 min) reminder trial (Suzuki et al., 2004). Also, when reminder trials were lengthened from 2.5 min to 15 min in mice, remote memories that were previously impervious became susceptible to disruption of reconsolidation (Frankland et al., 2006).

Much more research is needed before drawing definitive conclusions regarding the role of memory age on the utility of reconsolidation. For example, although stronger retrieval cues or repeated reminder trials may lead to reconsolidation of older memories, they may also inadvertently trigger extinction. As noted earlier, the use of protein synthesis inhibitors during extinction would block the consolidation of extinction, which could lead to the preservation of fear or craving. Furthermore, many of the pharmacological agents used in the studies listed above are toxic in humans. It is unclear whether purely behavioral methods for disrupting reconsolidation, such as following a brief reminder trial with an extended session of extinction training (e.g., Monfils et al., 2009; Schiller et al., 2009), would be effective with older memories. The possibility that older memories are less susceptible to reconsolidation disruption poses significant barriers to clinical application, as most individuals do not seek treatment immediately. In fact, it is most often years before individuals seek treatment (Christiana et al., 2000).

Context specificity

A number of sources point to contextual specificity in the disruption of reconsolidation. For example, "ABA" designs,

in which the acquisition and reminder trials are conducted in different experimental chambers (A and B) located in different laboratories (with the final test occurring in the original A chamber), fail to induce memory labilization and subsequent disruption in reconsolidation (Chan et al., 2010). Conversely, disruption in reconsolidation occurs when the acquisition context retains the majority of features of the original acquisition context (i.e., AA*A design) (Monfils et al., 2009).

Second, research using episodic memory paradigms in humans has failed to find disruption in reconsolidation when the reminder trials are conducted in a context different from that of initial learning. Hupbach, Hardt, Gomez, and Nadel (2008) asked participants to memorize a list of objects. After 48 hr, some participants were given a reminder trial, followed by learning a new list of objects. When participants were subsequently tested on their ability to recall items from the first list, those who had received the reminder trial showed increased intrusions of items from the second list. The authors interpreted this effect as reconsolidation-induced modification of the original memory (Hupbach et al., 2007). By varying features of the reminder context, such as the spatial context, the authors examined the necessary and sufficient conditions to induce memory lability. As in the fear conditioning studies described above, memory updating only occurred when the reminder trial occurred in the same physical context (i.e., the same room) as the initial learning (Hupbach et al., 2008).

Third, the disruptive effects of pharmacological agents such as anisomycin and propranolol (Kindt & Soeter, 2013; Nader et al., 2000) have been attributed partially to inhibition of amygdala and hippocampal processes (Schwabe et al., 2014). Thus, lesion and genetic knockout studies in animals, which directly inhibit hippocampal processing following a reminder trial, provide additional insight concerning the parameters that may constrain reconsolidation. For example, Winocur, Frankland, Sekeres, Fogel, and Moscovitch (2009) examined the effect of selective hippocampal lesions following context conditioning. Rats were conditioned in Context A and received a brief reminder trial (60 s) in either Context A or Context B prior to hippocampal lesions. Importantly, Context B mirrored the general contextual features of Context A but differed in specific features (e.g., size of the experimental chamber). All rats were later tested for freezing in Context A. Only rats that received the reminder in Context A prior to hippocampal lesions demonstrated disruption in reconsolidation. Winocur et al. suggested that contextual similarity between retrieval and original training was a necessary condition to induce hippocampus-dependent memory lability.

Similarly, mice lacking the immediate early gene *zif268* demonstrate deficits in long-term memory when a reminder trial occurs in the same context as initial learning, but demonstrate no deficits when a reminder trial occurs in a context that differs from initial learning (Bozon, Davis, & Laroche, 2003). *Zif268* is required for the reconsolidation of object recognition memory, and the failure to disrupt reconsolidation following reactivation in a different context suggests that contextual similarity is necessary to induce memory labilization (Bozon et al., 2003).

As stated, reconsolidation is thought to operate as an adaptive memory updating mechanism, allowing the integration of new information into previously consolidated memories (Hardt, Einarsson, & Nader, 2010; Tronson & Taylor, 2007). The degree of contextual similarity between original training and the reminder trial may serve as a "trigger" to determine whether to update the original memory or to create a new memory trace (Besnard, 2012; Chan et al., 2010). Indeed, neural models of the hippocampus suggest that similarity between retrieval and initial learning is a necessary condition in order to induce memory labilization (Osan, Tort, & Amaral, 2011).

On the other hand, several studies have induced memory lability in contexts that differ from initial training. For example, Nader and colleagues (Duvarci & Nader, 2004; Nader et al., 2000) have demonstrated disruption in reconsolidation via intracranial administration of anisomycin, using ABB and ABC designs. Procedural differences, such as the method of disruption (behavioral vs. pharmacological) or the type of Pavlovian memory (cued vs. contextual) may account for these disparate findings. For example, contextual specificity has been observed in both animals and humans when behavioral methods were used to disrupt reconsolidation (e.g., Chan et al., 2010; Hupbach et al., 2008). However, presenting the reminder trial in a context that differs from original training does not present a barrier to pharmacological disruptions in reconsolidation in animals (Duvarci & Nader, 2004; Nader et al., 2000). In addition, when the context itself serves as the CS, as in contextual fear conditioning, it may be necessary to re-present the original training context to induce memory lability (Winocur et al., 2009).

Additional research is needed to determine the precise factors that induce memory labilization. However, the sheer number of studies that have failed to induce memory lability in contexts that differ from initial training suggest that contextual similarity may pose a real constraint on reconsolidation. The one specific pharmacological approach that appears to disrupt reconsolidation independent of context (e.g., Nader et al., 2000) may have limited applicability for clinical treatment, given that anisomycin is toxic to humans and typically must be injected into the hippocampus or amygdala to exert its effect (Steinfurth et al., 2014).

In sum, evidence across species and methods of reconsolidation disruption suggests that contextual similarity between retrieval and initial learning may act as an important boundary condition on inducing memory lability and subsequent disruption in reconsolidation, particularly when using behavioral methods to disrupt reconsolidation or when the context acts as the CS. Presentation of the reminder trial in a context that differs from initial training may be insufficient to induce lability and instead may elicit the formation of a separate memory trace. Such contextual specificity presents a considerable challenge for clinical translation given that treatment almost always occurs in a context that differs from the initial acquisition context. For example, exposures and reminder trials in the treatment of PTSD typically occur in the clinic setting or in contexts that loosely resemble the original conditioning context (e.g., a dark room for an individual who survived a sexual assault) but rarely in the original training context. Similarly, treatment for substance use disorders rarely entails exposure to the precise contexts that may have served as conditional stimuli for drug administration. Furthermore, many individuals seeking treatment fail to recall the precise conditions under which they acquired their fear or addiction (Menzies & Clarke, 1995). Thus, it is nearly impossible to replicate the original conditioning context during treatment. Treatments in the real world typically mirror experimental "ABC" designs, in which acquisition occurs in one context and extinction and retest occur in other contexts. For example, a person may be sexually assaulted in one context, receive exposure therapy at a clinic, and then encounter an individual who resembles the perpetrator at a restaurant near their home. Research using ABA and ABC designs while parametrically varying features of the reminder context and method of disruption is needed to further establish the limitations that this potential boundary condition places on disrupting reconsolidation in humans.

Specificity in response systems

PTSD and anxiety disorders are characterized by several pathological processes that involve multiple response modalities, such as biases in attention, heightened physiological arousal and reactivity, and chronic avoidance of feared stimuli (Craske, 2003; Lang, 1971). Disrupting reconsolidation is often specific to particular response modalities. Research in humans has repeatedly demonstrated that pharmacological and behavioral disruptions in reconsolidation primarily affect physiological indices of fear as measured by the startle reflex while leaving US-expectancy ratings (i.e., judgments of the likelihood that a CS will be followed by a US) and skin conductance responses intact (Kindt & Soeter, 2013; Soeter & Kindt, 2011). Thus, though individuals demonstrate reduced reactivity to startle probes when confronted with the CS at test, their expectations of the aversive event and sympathetic arousal remain unaltered.

The failure of strategies that target reconsolidation to attenuate US expectancy or sympathetic arousal (let alone avoidant behavior, which has not been thoroughly evaluated in disruption of reconsolidation paradigms in humans) raises significant concerns about their ability to target psychopathology. For example, the extant literature on expectancy-based models of avoidance suggests that avoidant behavior is driven, in part, by knowledge regarding the relationship between the CS and US (Declercq, De Houwer, & Baeyens, 2008). In terms of reconsolidation, this may suggest that despite reduced startle reflexes in the presence of the CS, declarative knowledge of the CS–US relationship may still drive avoidant behavior and maintain pathology.

In addition, several studies have failed to demonstrate an effect of disrupting reconsolidation on inhibitory avoidance memories (See Appendix; e.g., Cammarota, Bevilaqua, Medina, & Izquierdo, 2004; Inda, Muravieva, & Alberini, 2011; Power et al., 2006). On the other hand, others have demonstrated disruptions in reconsolidation (e.g., Tronel & Alberini, 2007). Although classical Pavlovian paradigms have long been the experimental model for anxiety disorders, inhibitory avoidance paradigms may be critical models that complement Pavlovian models, given the strong behavioral avoidance component of PTSD and anxiety disorders (Craske, 1999). The parameters that permit versus restrain disruption of reconsolidation of inhibitory avoidance therefore provide yet another important target of research.

Similarly, appetitive conditioning, as an experimental analogue for drug addiction, results in numerous conditional behaviors including preference for the context in which a drug was given (CPP), approach toward Pavlovian signals (sign tracking; see Appendix), approach toward the area where the drug or reinforcer was given (goal tracking; see Appendix), and increased instrumental responding (effortful work/behavior) in order to obtain the drug. Each of these conditional behaviors can place an individual at risk for relapse following treatment for substance use disorders. For example, seeking out contexts and stimuli associated with drug use (CPP and sign tracking, respectively) or increased instrumental responses when in the presence of the drug (e.g., drug taking) may each lead to relapse. In order for disruption in reconsolidation to be an effective strategy for substance use disorders, it should mitigate both conditioned approach and instrumental behavior.

Research examining disruptions in reconsolidation across conditional responses has yielded mixed results. For example, the NMDA antagonist MK-801 disrupted Pavlovian but not instrumental responding in rats (Flavell

& Lee, 2013), and extinction within the reconsolidation window disrupted subsequent preference for the CS in rats who displayed sign tracking but not in those who displayed goal-tracking behavior (Olshavsky et al., 2013). Few studies have explored the impact of disruptions in reconsolidation on multiple conditional behaviors (sign tracking, goal tracking, CPP). Thus, future research is needed to determine the specificity of reconsolidation disruption on multiple response systems in both threat and appetitive conditioning.

Temporal stability

Some disruptions in reconsolidation appear to reverse with time or additional procedures. For example, although administration of anisomycin following retrieval of contextual fear reduces freezing at test 24 hr later, mice occasionally demonstrate renewal of the fear association when tested 21 days later (Lattal & Abel, 2004) or following an additional US presentation at test (Fischer, Sananbenesi, Schrick, Spiess, & Radulovic, 2004). Recently, Trent, Barnes, Hall, and Thomas (2015) demonstrated a return of contextual fear memory in rats following a US presentation despite using validated procedures to disrupt molecular processes thought to subserve memory reconsolidation (*zif268* and activity-regulated cytoskeletal-associated protein; Arc). This is important because both *zif268* and Arc have been demonstrated to be essential to reconsolidation, and the renewal of fear following a US presentation raises questions about whether or not reconsolidation results in the "erasure" of fear memories.

In appetitive conditioning, behavioral methods to disrupt reconsolidation (i.e., extinction) resulted in increased responding following rapid reacquisition (Millan et al., 2013). Rapid reacquisition involves re-pairing the CS and US following extinction and is an important experimental analogue for drug relapse. Given that the original fear was left intact, this has prompted debate regarding whether reconsolidation disrupts storage (e.g., erasure) or memory retrieval (e.g., diminished accessibility). Unfortunately, full consideration of this issue is beyond the scope of this article. Regardless of the mechanisms of the amnestic effect, the seemingly transient nature of reconsolidation disruption across laboratories using validated procedures raises questions regarding the utility of this strategy for long-term attenuation of fear or drug memories.

High trait anxiety

The majority of studies examining reconsolidation of fear memories have been conducted with either animals or healthy human populations. However, a wealth of research has demonstrated that individuals high in trait anxiety demonstrate deficits in associative learning mechanisms that may underlie reconsolidation processes. Using data collected across several studies, Soeter and Kindt (2013) reported that trait anxiety uniquely predicted the degree to which propranolol successfully disrupted reconsolidation. Disruption of reconsolidation was less successful in those with high trait anxiety, although the mechanistic underpinnings of this relationship are unclear. Given that repeated retrieval and reconsolidation enhances memory strength (Riccio, Millin, & Bogart, 2006) and that stronger memories have demonstrated some resistance to reconsolidation (Suzuki et al., 2004), ruminative processes, such as worry, may confer resistance to reconsolidation disruption.

A parallel effect has been observed in rodents. Chronically stressed rats show a resistance to disruptions in reconsolidation with rapamycin (which disrupts protein synthesis)—an effect that is mediated by the immediate early gene *zif268* (Hoffman et al., 2015). The authors argue that repeated traumatic stress serves as a more ecologically valid experimental analogue of PTSD than does standard Pavlovian conditioning, and the failure to demonstrate disruptions in reconsolidation in chronically stressed animals raises important questions regarding the translation of reconsolidation disruption into clinical interventions (Hoffman et al., 2015). Nonetheless, additional research is needed in order to elucidate the mechanisms through which trait anxiety and chronic stress may impact reconsolidation processes.

Reconsolidation: Looking Ahead

The emerging science of memory reconsolidation has changed the way we think about the long-term storage of associative knowledge, showcasing how the mere act of retrieving a memory can render that memory malleable and susceptible to modification. Efforts to experimentally disrupt reconsolidation via behavioral or pharmacological techniques have provided powerful demonstrations of the dampening, and perhaps even erasure, of specific memories for aversive associations. However, the degree to which disrupting reconsolidation is a viable clinical intervention remains questionable. Several boundary conditions have been identified, which may limit the impact of reconsolidation disruptions as a clinical intervention. First, the sheer number of studies that have failed to demonstrate reconsolidation across laboratories using validated procedures suggest that these boundary conditions pose true constraints on memory labilization, and, although reconsolidation may represent a fundamental property of some forms of memory, it may be far

less ubiquitous and consistent as previously thought. For example, Bos, Beckers, and Kindt (2014) failed to find any disruption in reconsolidation in humans despite using the exact same procedures (propranolol administration following a reminder trial) that their laboratory has previously used (e.g., Kindt & Soeter, 2013; Soeter & Kindt, 2011). Furthermore, there is a dearth of studies examining the interaction of multiple boundary conditions. Even if some boundary conditions can be overcome through procedural modifications (e.g., a stronger reminder trial for older memories), it is unclear whether additional boundary conditions would simultaneously mitigate memory labilization.

For example, an individual seeking treatment for PTSD may have spent years retrieving and rehearsing the original fear association (e.g., a sexual assault), thereby strengthening the memory trace. Treatment will entail exposure to generalization stimuli (e.g., individuals the same age and sex as the perpetrator) as opposed to the original stimulus, and reminder trials will occur outside of the original acquisition context (e.g., in the therapy room). Without clear guidelines, confrontation with a given feared stimulus may extend beyond the duration necessary to induce labilization and inadvertently trigger extinction. Although extinction may not be detrimental clinically unless combined with pharmacological agents, it fails to target the mechanisms of reconsolidation. In addition, the pathological fear network contains multiple CSs (e.g., physical intimacy, individuals the same age and sex as the perpetrator) and second order CSs (e.g., individuals consuming alcohol). Any disruption in reconsolidation will need to generalize to these various stimuli to be clinically meaningful.

Similarly, substance use disorders involve numerous conditional stimuli (e.g., drug paraphernalia, individuals who provided the drug) and contexts (e.g., locations where drug use occurred) as well as numerous conditional behaviors (sign tracking, goal tracking, CPP). The clinician is unlikely to have access to the original conditional stimuli and contexts, and any disruption in reconsolidation would need to generalize across multiple response systems in order to mitigate relapse.

In order for reconsolidation disruption to be a viable clinical intervention for PTSD, anxiety, and substance use disorders, it will need to overcome multiple boundary conditions. This may be one reason why preliminary clinical studies have produced mixed results, with some studies finding a benefit to pharmacological and behavioral disruptions in reconsolidation (Soeter & Kindt, 2015; Xue et al., 2012) whereas others failed to find any benefit (Wood et al., 2015).

Reconsolidation is thought to confer memory advantages, allowing the integration of new information into an established memory. The capacity of memory to be updated or strengthened following initial consolidation has numerous evolutionary advantages. For example, repeated memory labilization and reconsolidation may result in stronger memories for biologically significant events (e.g., food or danger). In addition, the incorporation of additional information during reconsolidation may facilitate updating of a memory, thereby allowing organisms to respond more effectively to changing environmental demands (Alberini & LeDoux, 2013). However, considering Pavlovian memories of threat and reward are essential to survival, there may be additional evolutionary advantage from constraining the updating of these memories to specific circumstances. For example, it is evolutionarily advantageous to protect memories of threat from constant updating unless specific circumstances (i.e., exact replication of the original learning) warrant the incorporation of new information.

The evolutionary advantage of protection from updating is consistent with the central theme of several of the boundary conditions mentioned above. We argued that reconsolidation might be constrained by the relationship between the stimuli and contexts during original learning and during the reminder trial. Stimuli and contexts that differ during the reminder trial compared to original learning are more likely to initiate discrimination and the formation of a new memory trace rather than memory lability. Constraining memory updating to stimuli and contexts that fully mirror those involved in original learning protects memories of threat and reward from constant updating and thereby preserves behavior that avoids threat (e.g., fear conditioning) and obtains reward (e.g., appetitive conditioning). However, this may also limit the clinical utility of reconsolidation disruption.

Research continues to delineate the molecular and neurobiological substrates of reconsolidation. However, additional experimental paradigms are required that more closely resemble clinical situations. We offer several suggestions for future research in order to more fully elucidate the parameters under which disruption in reconsolidation represents a viable clinical intervention.

1. Parametrically vary features of the reminder trial in order to determine how closely the reminder stimulus must match the original stimulus for memory lability to be induced: As discussed previously, reconsolidation may be constrained by the specificity of the reminder stimulus, such that only the original stimulus may induce memory labilization. Unfortunately, it is rare to have access to the original stimulus in clinical situations. Research that uses a range of generalization stimuli (e.g., stimuli that parametrically vary in their perceptual similarity to the original CS) will elucidate the effect of

stimulus similarity on memory lability. For example, in tests of fear generalization researchers have used stimuli that gradually change in size (Lissek et al., 2008) or faces that gradually morph (Onat & Büchel, 2015) to provide a gradient of stimuli. In addition, examining the effect of a generalization stimulus on inducing reconsolidation when presented in a context that differs from original learning will provide the most clinically valid test of reconsolidation.

2. Employ more ecologically relevant experimental paradigms: Reconsolidation research often employs simple Pavlovian fear or appetitive paradigms. However, clinical disorders likely involve multiple, complex, compound stimuli existing in an associative network. Although some research has examined reconsolidation using compound stimuli (Debiec et al., 2013), additional research is needed using ecologically valid learning paradigms, including the continued use of complex stimuli (e.g., compound stimuli) and immersive virtual reality contexts (e.g., Hone-Blanchet, Wensing, & Fecteau, 2014).
3. Duration of the reminder trial: As mentioned previously, the precise length or number of reminder trials necessary to induce reconsolidation appears to differ across experimental paradigms and type of memory (e.g., fear learning versus appetitive learning). In addition, the relationship between the reminder trial and the duration of CS exposure during initial conditioning may be important (Alfei et al., 2015). Future research should continue to examine the transition between reconsolidation and extinction in order to determine the precise duration or number of trials needed to induce reconsolidation across various experimental paradigms in humans (e.g., fear conditioning, contextual fear conditioning, inhibitory avoidance, appetitive learning).
4. Mental retrieval: Previous research has suggested that mental retrieval may be sufficient to induce reconsolidation (Hupbach et al., 2007). Unfortunately, the tendency of individuals to mentally retrieve the CS (e.g., worry or craving) may inadvertently extend the duration of the reminder trial and prevent reconsolidation. Further research examining whether or not mental retrieval is sufficient to induce memory lability and the effect of repeated mental retrieval prior to the presentation of a reminder stimulus will help clarify the impact of mental retrieval on reconsolidation.
5. Examine the effect of multiple boundary conditions: In order for reconsolidation to be a successful clinical intervention it will need to overcome multiple boundary conditions. For example, patients are likely to present with strong fear memories acquired years prior, and the clinician is unlikely to have access to the original conditional stimuli or contexts. Additive designs examining the effect of one, two, or multiple boundary conditions on inducing reconsolidation will be necessary before translating disruptions in reconsolidation to clinical populations.
6. Examine the effect on multiple response systems: Few studies have explored the impact of disruptions in reconsolidation on multiple conditional behaviors. For example, although disrupting reconsolidation of fear memory might reduce physiological reactivity, US-expectancy has been shown to remain intact (Soeter & Kindt, 2011). It is important to determine the effect of disrupting reconsolidation on multiple response systems. In fear conditioning paradigms, this would entail examining the impact of disrupting reconsolidation on physiological reactivity, US-expectancy, and avoidant behavior. In appetitive paradigms, this would include examining sign tracking, goal tracking, CPP, and instrumental responding simultaneously.
7. Durability: Although some research has examined the long-term durability of disruptions in reconsolidation, the results have been mixed. Several recent studies with humans have produced intriguing demonstrations that behaviorally induced (Björkstrand et al., 2015) or pharmacologically induced (Soeter & Kindt, 2015) manipulations of reconsolidation may diminish fearful associations (when the original stimulus is used to induce memory lability) for a year or longer. However, recent work in rodents has questioned the permanence of such effects and shown that contextual fear memories can ultimately re-emerge despite a complete blockade of hippocampal reconsolidation mechanisms (Trent et al., 2015). Additional research is needed that examines the long-term durability of disrupting reconsolidation using reinstatement, rapid reacquisition, and spontaneous recovery paradigms. This goes to the heart of the reconsolidation phenomenon regarding whether or not disrupting reconsolidation reflects permanent modification to the original memory (e.g., "erasure").

Appendix

Appetitive conditioning	A conditioning procedure where a neutral stimulus (conditional stimulus or CS) is repeatedly paired with a positive stimulus such as food or drug.
Conditioned place preference (CPP)	Appetitive conditioning paradigm in which a reinforcer (e.g., drug) is repeatedly administered on one side of a two-sided compartment. Animals will subsequently display preference toward the side of the compartment in which the reinforcer was administered.
Conditional stimulus (CS)	A neutral stimulus (e.g., tone) that predicts the occurrence of a biologically significant stimulus such as a drug or shock.
Extinction learning	Repeatedly presenting the CS in the absence of the US, or failing to reinforce instrumental behavior, leads to a reduction in responding as the animal learns either (a) that the CS no longer is the best predictor of the US or (b) that continued instrumental behavior will no longer lead to reward.
Goal tracking	In appetitive conditioning, animals may repeatedly approach the site where a reinforcer is delivered.
Inhibitory avoidance	In the typical inhibitory avoidance paradigm, a rodent is placed in a chamber containing a platform and an electrified grid. Stepping down from the platform onto the grid results in a shock. Extinction consists of repeated exposure to the grid in the absence of shock, and latency to step from the platform at a later test is an indicator of learned avoidance.
Reconsolidation	The process by which a memory is once again returned to a labile state and requires further protein synthesis in order to stabilize.
Reminder trial/Reactivation trial	A brief presentation of the CS/context that once again retrieves and destabilizes a memory.
Sign tracking	In appetitive conditioning, animals may show approach behavior to conditional stimuli that signal the likelihood of a reinforcer.
Unconditional stimulus (US)	Biologically significant stimulus such as food, drug, or shock.

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