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# Human Memory Reconsolidation: A Guiding Framework and Critical Review of the Evidence

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Research in nonhuman animals suggests that reactivation can induce a transient, unstable state in a previously consolidated memory, during which the memory can be disrupted or modified, necessitating a process of restabilization in order to persist. Such findings have sparked a wave of interest into whether this phenomenon, known as reconsolidation, occurs in humans. Translating research from animal models to human experiments and even to clinical interventions is an exciting prospect, but amid this excitement, relatively little work has critically evaluated and synthesized existing research regarding human memory reconsolidation. In this review, we formalize a framework for evaluating and designing studies aiming to demonstrate human memory reconsolidation. We use this framework to shed light on reconsolidation-based research in human procedural memory, aversive and appetitive memory, and declarative memory, covering a diverse selection of the most prominent examples of this research, including studies of memory updating, retrieval-extinction procedures, and pharmacological interventions such as propranolol. Across different types of memory and procedure, there is a wealth of observations consistent with reconsolidation. Moreover, some experimental findings are already being translated into clinically relevant interventions. However, there are a number of inconsistent findings, and the presence of alternative explanations means that we cannot conclusively infer the presence of reconsolidation at the neurobiological level from current evidence. Reconsolidation remains a viable but hotly contested explanation for some observed changes in memory expression in both humans and animals. Developing effective and efficient new reconsolidation-based treatments can be a goal that unites researchers and guides future experiments.

***Public Significance Statement***
In this critical review we formalize a framework for the evaluation and design of studies of memory reconsolidation in humans. Synthesizing research across memory types, we find considerable evidence consistent with human memory reconsolidation. However, significant gaps in the evidence base remain for most types of memory studied. We suggest that clinically relevant research geared toward the development of reconsolidation-based treatments can unite researchers in the field.

*Keywords:* memory reconsolidation, clinical applications of reconsolidation, procedural memory, declarative memory, emotional memory



The predominant model of memory formation posits that memories can transition from a short-term, relatively unstable state, to a more robust, long-term form (McGaugh, 2000). This process, known as consolidation, is most commonly thought to be mediated by changes at the synaptic level, such as long-term potentiation (LTP) and long-term depression (LTD; Kandel, Dudai, & Mayford, 2014; Nader & Hardt, 2009). Shortly after learning, interventions such as the administration of protein synthesis inhibitors appear to block the development of these synaptic changes, thereby preventing the consolidation of the memory (Schafe & LeDoux, 2000). Once this cellular consolidation process has taken place, memories are generally insensitive to such manipulations.

Despite the relative permanence of consolidated memories, it is clear that memories can be forgotten or can undergo changes over time. Indeed, early memory researchers found that the same amnestic treatments that prevented the consolidation of memories could also produce amnesia if delivered following memory reactivation (reviewed in Sara, 2000). For example, Misanin, Miller, and Lewis (1968; see also Schneider & Sherman, 1968) found that an electroconvulsive shock (ECS) delivered after the reactivation of a consolidated memory for fear conditioning produced as profound a degree of amnesia as when the ECS was delivered during

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initial consolidation. Without memory reactivation, ECS had no effect. Hence, it appeared that reactivation induced a transient state of vulnerability in an otherwise consolidated memory trace. Rubin (1976) made an early attempt to harness this newly discovered malleability of memory in the treatment of psychiatric disorders, apparently with some success. Twenty-eight treatment resistant patients with delusions, compulsions, obsessions, or hallucinations reactivated their pathological cognitions or behaviors, and then received contemporaneous ECS while still awake. These patients were reported to experience relief from their symptoms, some for as long as 10 years. However, more controlled studies cast doubt on the possibility that human memories could be made vulnerable to amnestic agents following reactivation (Squire, Slater, & Chace, 1976).

Since these early studies, interest in the phenomenon of retrieval-induced memory lability in humans appears to have largely waned until the work of Sara and colleagues (Przybyslawski & Sara, 1997; Sara, 2000) and Nader, Schafe, and LeDoux (2000) refocused attention on the topic in animal models under the name of reconsolidation (cf. Spear, 1973, p. 188). In a pair of influential studies, Schafe and LeDoux (2000) first demonstrated that the administration of anisomycin (a protein synthesis inhibitor) to the amygdala shortly, but not 6 hr after fear conditioning, blocked the consolidation of the memory. Hence, there appeared to be a time-dependent state of memory consolidation, during which the nascent memory trace was vulnerable to interference. Nader et al. (2000) extended these findings by showing that reactivation of a consolidated memory trace temporarily returned it to a similar state, during which anisomycin could likewise produce amnesia for the learned fear response.

Such reactivation-dependent effects of amnestic agents have now been demonstrated in a range of model organisms, from fish, to crabs, to rats (Eisenberg, Kobilo, Berman, & Dudai, 2003; Nader et al., 2000; Pedreira, Pérez-Cuesta, & Maldonado, 2002) and for a range of memory types (Dudai, 2006). Given the conservation of brain processes across the phylogenetic scale, these findings have stimulated a renewed interest in the possibility that human memories might also undergo a process of reconsolidation.

Excitement over the prospect of memory reconsolidation in humans is warranted: Reconsolidation may greatly change how we understand memory and provide scope for novel clinical approaches. However, amid this enthusiasm, relatively little work has critically evaluated and synthesized research claiming to demonstrate reconsolidation in humans across memory types, and clear criteria for evaluating reconsolidation as a candidate mechanism have not been consistently applied. For the field to progress, a clear understanding of current evidence for reconsolidation in humans, as well as its limitations, is essential. A framework upon which compelling future research can be built is also needed. In this article, we first formalize a framework, based on animal models of reconsolidation, for evaluating and designing reconsolidation-based research. We then use this framework to highlight and critique a selection of reconsolidation-based studies, reflecting a diverse array of human memory systems, with a particular focus on paradigms with which multiple experiments have been conducted. We consider studies of procedural memory, aversive and appetitive memory, and declarative memory (for those interested only in particular types of memory, each section is written so as to be intelligible if read in isolation from the other sections). For each of these areas, we discuss conflicting findings and alternative explanations, and highlight practical and/or clinical applications of the findings. We conclude with a summary of the evidence for reconsolidation across these fields, and discuss the challenges and prospects facing reconsolidation-based research.

## A Framework for Reconsolidation Research in Humans

A clear recommendation for research aiming to provide evidence for reconsolidation in humans is that it should utilize the canonical 3-day design used in animal research on reconsolidation, consisting of learning (Day 1), memory reactivation, possibly with an experimental manipulation (Day 2), and testing (Day 3; Nader & Hardt, 2009; Tronson & Taylor, 2007). These three days need not be consecutive, but a multiple day design allows for the consolidation of the newly learned memory, which is clearly obligatory for a demonstration of reconsolidation, as one might otherwise simply be interfering with the initial process of consolidation. It should be noted that after 24 hr, the process of consolidation is not strictly complete, as further changes to the neural substrate of memories do occur with the further passage of time (Squire, 1986). Waiting for 24 hr does, however, ensure the presence of a long-term memory trace. Where reconsolidation-based clinical interventions are concerned, or where reconsolidation of preexisting autobiographical memories is being tested, the target memory is already present and so Day 1 learning is unnecessary. Testing for the impact of a reconsolidation-based manipulation should occur on a separate day to that manipulation (in addition to possibly testing for immediate effects), in order to allow time for the putative restabilization of the memory trace.

There are a number of observations that can be seen as consistent with the process of reconsolidation (Dudai, 2006; Nader & Hardt, 2009; Tronson & Taylor, 2007). These are derived from the definition of reconsolidation as the reactivation-dependent induction of a transient, unstable state of a previously consolidated memory, during which the memory trace may be modified or disrupted, and requiring a time-dependent process of restabilization in order to persist. Their demonstration may require a number of control groups and testing on different days to the standard 3-day reconsolidation design. In addition to criteria derived from this descriptive level (1–3 below), from a neurobiological perspective, it is commonly supposed that the structural modification of neuronal networks that maintain a memory engram requires de novo protein synthesis (Schafe & LeDoux, 2000), and that such protein synthesis is also necessary for reconsolidation once a memory has entered a labile state (Nader et al., 2000). However, the memory has been found to be functional (i.e., successful retrieval can occur) shortly (4 hr) after reconsolidation-based disruption, with protein synthesis dependent effects only being observed at later testing (Nader et al., 2000). This consideration leads to Criterion 4.

1. Reactivation × Manipulation interaction: If there is an experimental manipulation intended to affect the reactivated memory, then there should be an interaction between reactivation and this experimental manipulation, such that reactivation alone, or the manipulation without reactivation, have no effects on the outcome measure, or

that their independent effects could not simply be summed to produce the effect of both in combination.

2. Time dependency: An experimental manipulation that is supposed to affect the reconsolidation of a memory should have no such effect if performed outside the reconsolidation window (thought to be at most 6 hr after reactivation in animal models of fear conditioning; Nader et al., 2000).

3. Memory specificity: The experimental manipulation should affect the reactivated memory trace, rather than producing a general amnestic effect.

4. Dissociation of immediate and delayed effects: The effects of reconsolidation-based interventions will be most convincingly shown when disclosed at long-term testing but not shortly after the experimental manipulation, due to the putative retention of a functional memory trace that was formed previously.

Using such a framework, it is possible to assess the degree to which outcomes of human studies parallel those of animal studies that are taken as particularly strong evidence for reconsolidation. However, these criteria deserve some additional comment.

A Reactivation × Manipulation interaction can be understood as a statistical criterion that technically requires the use of 2 × 2 experimental design: reactivation (yes/no) and manipulation (yes/no). When reviewing studies of reconsolidation, it is clear that many studies have not followed this design in order to clearly demonstrate a significant interaction. In particular, a condition in which both reactivation and a manipulation are absent is often lacking. Such designs do not allow for a clear demonstration of a significant statistical interaction. However, in many experimental paradigms, it is already well established that in the absence of any reactivation or manipulation, the memory trace is unaffected over the short time periods used in most studies of reconsolidation (e.g., memories for Pavlovian conditioning can be maintained for long time periods without interventions). It should also be considered what the specific study is aiming to demonstrate or test, and whether previous studies using the same paradigm have already provided evidence of an interaction. Not all studies of reconsolidation are simply aiming to show an interaction, and may be intended to examine boundary conditions on the induction of reconsolidation or a host of other informative questions. The use of multiple control groups to demonstrate an interaction, or to test for other criteria, may be redundant or inappropriate.

In other paradigms, such as when new learning is used as a manipulation, the outcome variable may be dependent upon material given in the manipulation (e.g., the intrusion of newly learned material into recall of older memories). In some such experiments, a "no manipulation" condition may be irrelevant, as there is no plausible way for unknown material to intrude upon older memories. In still other cases, researchers have aimed to control for the impact of specific types of reactivation by comparing them with alternate, ineffective means of reactivation, rather than with "no reactivation" controls. Such factors complicate interpretations as to whether an interaction is present, and it may make more sense to consider whether effects are reactivation-dependent, or dependent upon the type of reactivation, rather than requiring a Reactivation × Manipulation interaction.

Rather than simply dismissing these cases as failures to demonstrate an interaction between reactivation and a manipulation, in the following discussion of studies and in the respective tables we have aimed to make inferences as to whether outcomes likely reflect an interaction based upon the conditions used in the experiment and what is known from other research. For example, if a study claiming an interaction neglected one of the control conditions necessary for a 2 × 2 design, yet a substantial body of evidence outside the field of reconsolidation indicates that the memory is unaffected in such a condition, or affected in such a way that makes additive effects of the control conditions an unlikely explanation for the claimed interaction effect, we have suggested that it may be reasonable to infer the presence of an interaction. Notation in the tables identifies cases where we believe such an inference might be reasonable. Nevertheless, especially where novel or relatively unstudied paradigms are used, we would encourage researchers to utilize a 2 × 2 design, and to conduct appropriate statistical tests for determining a Reactivation × Manipulation interaction. Furthermore, researchers should seriously consider the power of their experimental designs, as providing evidence for a statistical interaction between conditions typically requires quite large sample sizes, especially where relatively small effects are concerned. Where there is a failure to find evidence of an interaction, it may also be advisable to supplement traditional "null hypothesis significance testing" approaches with Bayesian analyses, which can determine whether the data provides evidence in favor of the null (*against* the presence of an interaction), rather than just determining that statistical significance was not reached.

Regarding time dependency of experimental manipulations, several possible complications are worth considering. First, in pharmacological interventions, due to the specific pharmacokinetics of many drugs used, the drug is often administered before memory reactivation. This allows the drug to reach peak levels within the reconsolidation window. It should be stressed that with such manipulations, the intervention is the presumed presence of the drug in the participants' brain, rather than the act of swallowing a pill, and so prereactivation drug administration may still be understood as an intervention occurring within the reconsolidation window. However, due to the higher number of alternative explanations for reactivation-dependent drug effects when drugs are administered before reactivation (e.g., a long-lasting impact on retrieval), postreactivation drug administration is optimal if a mechanistic understanding of the intervention is the aim of a study. Second, in tests of manipulations administered outside of the reconsolidation window, it is ideal if the manipulation is still given on the same day as reactivation. This is because sleep-related changes to memory may cause an intervention to have different effects when administered on a different day to reactivation, versus when given on the same day but outside of the reconsolidation window (see Sara, 2017 for a review of the impact of sleep on memory). Third, in some studies, a manipulation may have an effect but only when given very shortly after reactivation. In such cases, the manipulation may be time dependent, but not in a manner that is entirely consistent with reconsolidation, which is generally understood to refer to a labile state of memory that lasts on the order of hours rather than seconds. In such cases, researchers should try to ex-

plain how the observed effects can be understood in terms of reconsolidation.

Where all criteria are met, it should be stressed that there are serious limitations to our ability to infer the presence of a neurobiological process such as reconsolidation, and particularly to infer specific neurobiological mechanisms such as protein synthesis dependence, without direct access to the neurobiological substrate. Drawing on De Houwer's (2011) critique of the use of behavioral effects as proxies for mental constructs in cognitive psychology, we might say that for a behavioral effect to stand in for a neurobiological process, it is not enough that the effect can be explained in terms of that process. To allow for strong reverse inferences from a behavioral effect to a neurobiological process, the process must be a necessary condition for the effect. If there are alternative explanations for an observed behavioral effect, then we cannot make a strong inference from the presence of a behavioral effect to the presence of the neurobiological process.

Hence, so long as alternate explanations for observations of postreactivation amnesia exist, assessments based on the above criteria can only indicate that findings are consistent with, and cannot be seen as proof of, reconsolidation, or of specific neurobiological models of this process. With respect to Criterion 4, for example, there are alternative explanations that do not rely on protein synthesis dependent reconsolidation, or on reconsolidation-like phenomena at all, as to why intervention effects might only be observed at delayed testing (Riccio, Millin, & Bogart, 2006; Sederberg, Gershman, Polyn, & Norman, 2011, see the Alternative Explanations sections for Pharmacological Blockade of Aversive and Appetitive Memory Reconsolidation and Declarative Memory Reconsolidation below). Conversely, it is conceivable that, in addition to reconsolidation, other processes may be engaged by an experimental manipulation that produce changes in memory expression at short-term testing. Therefore, the presence of an effect of a reconsolidation-based manipulation at short-term testing cannot strictly rule out the possibility that reconsolidation explains the later effects. Of course, if there were no differences between the induction of these other processes and the induction of these processes *plus* reconsolidation, it would be unnecessary to invoke reconsolidation as an explanation.

Given these considerations, the framework proposed should be considered a basis for understanding how previous studies might align with the idea of reconsolidation, and how compelling future studies can be designed, but not as providing definitive conclusions as to whether an observed effect represents reconsolidation or not. It is also possible for the framework to be built upon and adapted as we gain further understanding of memory. We stress, therefore, that while these are valid and meaningful criteria, understanding the evidence for reconsolidation in humans requires a nuanced consideration of individual studies and paradigms as well as what they are aiming to demonstrate or test, and is not a simplistic "box ticking" activity. The summary tables we provide are thus meant as guides to the broader discussion in the text, rather than definitive assessments to be taken in isolation.

With this framework (and its caveats) in mind, and with an eye toward the consideration of alternative explanations, in the following sections we synthesize research into human memory reconsolidation across a range of memory types and experimental paradigms.

## Procedural Memory Interference

**Experimental studies.** The first modern study to demonstrate reconsolidation-like effects of interventions in humans used a procedural memory paradigm (Walker, Brakefield, Hobson, & Stickgold, 2003a). In this influential study, Walker, Brakefield, Hobson, and Stickgold (2003a) demonstrated that after initial learning of a finger-tapping sequence, the motor memory was susceptible to interference from learning a competing sequence shortly, but not 6 hr afterward. Hence, there appeared to be a period of memory stabilization. This period of stabilization was followed by an overnight enhancement in accuracy (offline gains). However, Walker et al. (2003a) found that the stability of the first motor sequence could be reversed if participants were required to briefly rehearse the sequence prior to learning a second finger-tapping task. This new learning did not immediately disrupt the memory for the initial sequence, as shown by intact performance of Sequence 1 when tested shortly after participants learned the interfering sequence. Rather, accuracy for the first sequence was only reduced following a night of sleep, whereas performance for the second sequence improved.

These findings suggest that a procedural memory undergoes an initial process of stabilization over 6 hr and enhancement over a night of sleep, reflecting a process of consolidation. However, it appears that a consolidated motor memory can be destabilized following reactivation, requiring a process of restabilization to prevent interference from competing motor learning. These results were found using the 3-day design necessary to demonstrate a clear reconsolidation effect in experimental studies (Day 1 learning, Day 2 reactivation and interference, Day 3 testing), suggested a Reactivation $\times$ Manipulation interaction (though a control group in which no reactivation or new learning occurred was not used, other research found that memory is enhanced over multiple nights of sleep without reactivation or interference: Walker et al., 2003b), and also a dissociation of immediate and delayed effects of the postreactivation manipulation. Hence, the findings display a clear, though incomplete (lacking demonstrations of time dependency and memory specificity), parallel to research in animal models used as evidence for reconsolidation.

Since this early demonstration, however, relatively few studies have tackled the issue of reconsolidation in human procedural memory. Censor and colleagues confirmed that motor memories underwent offline gains after both initial learning and reactivation (Censor, Dimyan, & Cohen, 2010). They also showed that repetitive transcranial magnetic stimulation (rTMS) delivered to the primary motor cortex (M1) *during* reactivation prevented the development of these offline gains, relative to stimulation of the vertex (a control or "sham" stimulation region), or ulnar nerve stimulation that disrupted actual performance in a manner similar to M1 stimulation. Although these findings indicate that offline gains can be blocked as a result of M1 interference, they do not provide convincing evidence of reconsolidation, or corroborate the results of Walker et al. (2003a).

First, Censor, Dimyan, and Cohen (2010) did not include an assessment of performance when M1 stimulation was given without reactivation, meaning that a Reactivation $\times$ Manipulation interaction cannot be firmly established. Second, M1 stimulation contemporaneous with reactivation presents further challenges for interpretation, as it could be that this affects some form of new

encoding that takes place during retrieval or practice. Animal research on fear conditioning in fact suggests that reconsolidation or other memory processes are not actually triggered during reactivation, but only once reactivation is completed and the organism is removed from the reactivation context (Pedreira & Maldonado, 2003; Pérez-Cuesta, Hepp, Pedreira, & Maldonado, 2007). An ideal test would therefore be to perform M1 stimulation shortly after reactivation, when the memory would be expected to have entered a labile state. Given that the outcomes of postretrieval M1 stimulation, or M1 stimulation without reactivation are unknown, these findings do not provide convincing evidence for reconsolidation. Moreover, Walker et al. (2003a) found an actual decrease in performance after interference, suggesting some kind of modification to the detriment of the original memory, whereas Censor et al. (2010) only observed a failure of the memory to undergo offline enhancement. This indicates that M1 stimulation prevented any benefits from rehearsal, but not that the original memory was disrupted or updated.

Hardwicke, Taqi, and Shanks (2016) could not find support for the findings of Walker et al. (2003a) in a series of attempted replications. While Hardwicke et al. (2016) did observe the offline gains that have been consistently shown across studies, reactivation followed by new learning did not produce any performance deficits when tested a day later. While it has been suggested that this failure to replicate could reflect differences in experimental design, the participant pool, or boundary conditions on reconsolidation (Walker & Stickgold, 2016), it is worth noting that some possible moderating variables (session time, participant age) were tested by Hardwicke et al. (2016) and found to bear no relation to the outcome.

It is clear that there can be factors that limit or prevent the induction of reconsolidation (known as boundary conditions; Elsey & Kindt, 2017a). However, one study demonstrating a relationship between session timing (a suggested boundary condition for procedural memory) on the production of reactivation-induced interference did not show a robust, reconsolidation-like effect (de Beukelaar, Woolley, & Wenderoth, 2014). de Beukelaar et al. (2014) found that acquiring an interfering motor sequence after reactivating the previously consolidated sequence produced a drop in performance the next day, and that this effect was linearly related to the length of the reactivation. The longer the reactivation, the less of an impact subsequent learning had. Yet, these effects appeared only for the first trial of testing, after which performance quickly recovered. This suggests that the original memory was probably not directly modified or disrupted, but very briefly inaccessible. No control group was included to assess the impact of new learning in the absence of any kind of reactivation, and whereas previous studies showed an impact of interference on accuracy and not speed, de Beukelaar et al. (2014) found a significant effect on speed but not accuracy. Subsequently, de Beukelaar, Woolley, Alaerts, Swinnen, and Wenderoth (2016) found that not just the length of reactivation, but time from reactivation to new learning, determined whether interference effects were observed. Participants all received a reactivation of the motor tapping task on Day 2, and then waited 0 s, 20 s, 40 s, or 60 s before learning a second sequence. Results suggested a deterioration in the speed, but not accuracy, of performance for the 20-s group only, and this effect was again observed only on the first trial of testing on Day 3.

**Practical and clinical implications of procedural memory reconsolidation.** Although studies investigating the reconsolidation of human motor memories can inform our theoretical understanding of how such memories change over time, there appear to be relatively few clinical implications of procedural memory research. Given that procedural memories rely upon at least partially distinct brain systems to those supporting emotional memory (Squire, 2004), conclusions drawn as to the malleability of motor memories cannot be extended to disorders of emotional memory. Though some disorders do feature uncontrollable movements (e.g., motor tics) or compulsive actions (e.g., hair pulling in trichotillomania) as major components, we are not aware of any psychiatric disorders characterized solely by maladaptive learned motor behaviors. There may be some relevance of these lines of research if they could be extended to model aspects of these disorders or even intervene in such cases, but research is far from this stage at present.

From a more general practical perspective, many sports and musical performances involve learning and repeatedly practicing highly complex and precise motor movements. Reconsolidation-based research on motor memories may be able to aid in the determination of optimum training procedures, in order to facilitate enhanced speed and accuracy, as well as preventing confusion between different learned behaviors. There is even space for research on "neuroenhancement" of such skills, if pharmacological or brain stimulation procedures could affect performance when administered after reactivation. However, current studies present a mixed picture as to the lability of motor memories after reactivation in normal experimental subjects, and we are not aware of any research that has assessed reactivation-dependent changes in memory expression for professional sportspeople or musicians (musicians are often excluded in procedural memory research).

**Summary of procedural memory reconsolidation.** Table 1 provides an overview of studies on reconsolidation in procedural memory. In summary, the research of Walker et al. (2003a) suggested the presence of a Reactivation × Manipulation interaction, as well as the dissociation of immediate and delayed effects, showing clear parallels with the putative phenomenon of reconsolidation in animal models. However, studies using similar designs have failed to replicate these effects, and other procedural memory disruption studies do not clearly corroborate the idea that reactivation destabilizes such memories and necessitates a process of restabilization. There are many possible reasons why subsequent studies might fail to replicate Walker et al.'s (2003a) original findings, and it would be rash to assume this study merely represents a false positive. However, reasons for a failure to replicate, such as boundary conditions, are conjectural and should be directly tested if reconsolidation of human procedural memories is to be fully understood, or indeed firmly demonstrated to occur. One study has provided evidence consistent with time dependent effects (de Beukelaar et al., 2016), but it should be noted that the time period suggested was highly specific and brief, that performance recovered after the first trial, and there was no control for general effects of new learning without reactivation. Demonstration of further reconsolidation criteria, such as by initially learning two motor sequences and then only reactivating and manipulating one of them (to show memory specificity) is also desirable.

Table 1
*Reviewed Studies of Procedural Memory*

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Censor, Dimyan, & Cohen, 2010 | Finger sequence tapping task | rTMS to M1 | During reactivation | — | — | — | — | rTMS to M1 versus sham stimulation after reactivation prevented offline gains. Did not include controls for reactivation versus no reactivation. |
| de Beukelaar et al., 2014 | Finger sequence tapping task | New learning | Shortly after reactivation | ~RTD | — | — | — | Short (but not long) reactivations followed by new learning produced a deficit in performance on the following day, but only for the first trial of testing. |
| de Beukelaar et al., 2016 | Finger sequence tapping task | New learning | Shortly after reactivation | — | ~Yes | — | — | Impairment of speed was observed on the first test trial when new learning took place 20 s, but not immediately, 40 s, or 60 s after reactivation. Effects were limited to the first trial of testing. There were insufficient controls to determine the presence of a Reactivation × Manipulation interaction. |
| de Beukelaar et al., 2014 | Finger sequence tapping task | New learning | Immediately, 20 s, 40 s, & 60 s after reactivation | ~RTD | — | — | — | Short (but not long) reactivations followed by new learning produced a deficit in performance on the following day, but only for the first trial of testing. |
| Hardwicke, Taqi, & Shanks, 2016 | Finger sequence tapping task | New learning | Shortly after reactivation | No | — | — | — | Four attempted replications of reactivation-dependent interference of procedural memories were unsuccessful. |
| Walker, Brakefield, Hobson, & Stickgold, 2003a | Finger sequence tapping task | New learning | Shortly after reactivation | Yes* | — | — | Yes | New learning after reactivation reduced accuracy at delayed but not immediate testing. No control for no reactivation + no manipulation was used, but other research suggests memory is enhanced when tested days after learning without reactivation or interference—the opposite of the effect observed when reactivation and new learning are combined. |

*Note.* 1 = Reactivation × Manipulation interaction; 2 = Time dependency; 3 = Memory specificity; 4 = Dissociation of immediate and delayed effects; — = not assessed; RTD = effects were dependent upon the type of reactivation; M1 = primary motor cortex; rTMS = repetitive transcranial magnetic stimulation.
~ Represents that a criterion may have been imperfectly demonstrated, or that the interpretation of this demonstration as being consistent with reconsolidation is uncertain (e.g., if observed memory impairments rapidly recover). Reasons are discussed in the summary column and in the main text. * Represents that we believe there is sufficient ground to infer a reactivation × manipulation interaction in a study, but that a strict 2 × 2 ANOVA with a test for an interaction was not conducted.

## Aversive and Appetitive Memory Reconsolidation

### Pharmacological Blockade of Aversive and Appetitive Memory Reconsolidation

**Experimental studies.** An obvious rationale for studying the reconsolidation of aversive and appetitive memories in humans is to develop more effective strategies to persistently change undesired and excessive emotional memories. Although extinction learning is one of the most extensively studied and effective procedures to reduce learned affective responses, in many cases people experience relapse. Extinction essentially involves repeated exposure to conditioned stimuli without the aversive (or rewarding) consequences. As a result, the conditioned stimuli gain new predictive properties. Fear-conditioning research in animals and humans has reliably shown that even after successful extinction training, the conditioned fear response can be easily recovered through the use of memory retrieval techniques: reexposure to unsignaled unconditioned stimuli (USs; i.e., reinstatement), a context change (i.e., renewal), or testing several weeks later (i.e., spontaneous recovery; Bouton, 2002). A consensus has been reached that extinction learning does not primarily operate through modifying the original fear memory, but instead through the formation of a new inhibitory memory (Bouton, 2002; Craske et al., 2008). This extinction memory competes for behavioral control at retrieval, thereby suppressing the fear responding driven by the original fear memory. In contrast, by capitalizing upon the phenomenon of reconsolidation, it may be possible to modify the strength of the original memory, overcoming known limitations of extinction-based approaches.

Many animal studies have been conducted using pharmacological agents such as anisomycin to block protein synthesis following memory reactivation and thereby provide evidence for a protein synthesis dependent phase of reconsolidation (Nader & Hardt, 2009). Given the use of such procedures across a range of animal models and memory paradigms (Eisenberg et al., 2003; Nader et al., 2000; Pedreira et al., 2002), pharmacological blockade of reconsolidation in human studies is a promising translational approach.

Clearly, potent neurotoxic drugs such as anisomycin would be unsuitable for use in humans, but alternative amnestic agents that block receptors that are believed to facilitate or be necessary for protein synthesis are available (Gelinas & Nguyen, 2005; Kindt, 2014). Debiec and LeDoux (2004) found that propranolol, a beta-adrenergic receptor (β-AR) antagonist commonly administered for the treatment of hypertension, blocked the reconsolidation of an auditory fear memory when infused into the amygdala of rats after memory reactivation. Crucially for the prospect of using propranolol in humans, for whom targeted drug delivery is only possible under extraordinary circumstances, Debiec and LeDoux (2004) also found that systemic administration of the drug was equally effective. β-ARs play an important role in plasticity related protein synthesis via the downstream β-AR/protein kinase A (PKA)/cAMP response element binding protein (CREB) signaling pathway, one of the molecular cascades that regulates the gene transcription required for the consolidation and reconsolidation of memory (Kandel, 2012; Otis, Werner, & Mueller, 2015). Hence, it is thought that propranolol may exert its influence over memory reconsolidation by inhibiting noradrenaline-stimulated CREB phosphorylation in the amygdala, which would indirectly disrupt protein synthesis (Kindt, 2014; Thonberg, Fredriksson, Nedergaard, & Cannon, 2002).

The translational feasibility of this approach has been demonstrated in multiple studies of Pavlovian fear conditioning in humans. In the first study to demonstrate this effect, participants underwent a differential conditioning procedure, in which they learned to associate two different fear-relevant stimuli (pictures of spiders, which are argued to have posed a survival threat to ancestral humans) with either an unpleasant electrical shock, or with the absence of shock, on Day 1 (Kindt, Soeter, & Vervliet, 2009). The primary outcome measure was fear-potentiated startle (FPS), a defensive reflex observed across mammalian species, and often used as an index of the negative valence attributed to a stimulus after conditioning (P. M. Bradley & Galal, 1988; Brown, Kalish, & Farber, 1951). On Day 2, two groups of participants were given either 40 mg of propranolol or placebo 90 min before a memory reactivation session, to allow peak bioavailability of the drug during the period of reconsolidation immediately following retrieval (Gilman & Goodman, 1996). In the reactivation session, participants expected to undergo a second day of training. In fact, the conditioned stimulus (CS)+ from the day before was presented just once and without a shock, and the experiment was then terminated. A third group received propranolol on Day 2 without a reactivation session, while being in the same experimental room where the original fear learning took place. On Day 3, participants' responses to each stimulus were tested in the absence of any shocks over 10 extinction trials, followed by a reinstatement test.

Whereas participants in the placebo + reactivation and the propranolol only groups displayed heightened startle responses to the CS+ relative to the CS− on Day 3, those in the propranolol + reactivation group showed durably low startle responding to the CS+ from the first to the last trial of extinction. Moreover, an established reinstatement procedure—the presentation of unsignaled shocks—failed to recover differential responding in the propranolol + reactivation group, whereas extinction learning on Day 3 was quickly reversed by this procedure in the other two groups. These results provide a clear demonstration of a Manipulation × Reactivation interaction. Though no group receiving neither reactivation nor propranolol was used, other work demonstrates that startle responses are not neutralized, nor resistant to reinstatement, in the absence of reactivation and propranolol (Soeter & Kindt, 2011).

These basic findings have since been replicated in several studies (Soeter & Kindt, 2010, 2011, 2012a). In addition to replicating the basic propranolol + reactivation effect, it has been demonstrated that this effect is specific to the reactivated memory (e.g., Soeter & Kindt, 2011, 2012b). Participants in these studies were trained to associate two different stimuli with electric shocks, and then only one of these stimuli was presented on Day 2, followed by propranolol. On the third day of testing, startle responses to the reactivated stimulus had been neutralized, whereas fear potentiated startle for the nonreactivated stimulus was still present. Hence, it is clear that propranolol does not simply cause general amnesia.

In support of the idea that these apparently reconsolidation-based effects might be preferable to outcomes observed in standard extinction, it was found that there was no spontaneous recovery of fear responses in the reactivation + propranolol group after 1 month (Soeter & Kindt, 2010). In addition, fear responses after

reconsolidation blockade were not renewed by changes in context (Soeter & Kindt, 2012a). Finally, even when the CS was paired again with an aversive US, reacquisition of the fear-potentiated startle was no more rapid than when the original learning took place, suggesting that the memory was so weakened by the procedure as to leave no savings of the memory (Soeter & Kindt, 2011). In contrast, merely extinguished memories show accelerated reacquisition, due to the putative retention of the memory for the original learning experience. Although these behavioral observations cannot be explained by extinction, they do not themselves provide proof of reconsolidation, or for the complete removal of the memory trace (see Alternative Explanations and Long-term Effects of Reconsolidation-based Interventions sections below).

Interestingly, participants receiving propranolol + reactivation have been found to retain their declarative memories for the conditioning procedure (Kindt et al., 2009; Soeter & Kindt, 2010). Furthermore, while reactivation + propranolol has been found to neutralize differential startle responses, differential skin conductance responses are typically maintained (Soeter & Kindt, 2010). Skin conductance is far more responsive than startle to contingency knowledge and nonspecific arousal (Bradley, Cuthbert, & Lang, 1999; Sevenster, Beckers, & Kindt, 2012a; Sevenster, Beckers, & Kindt, 2014a). In contrast, the startle response appears to track the emotional valence of a stimulus. These results therefore suggest that propranolol combined with reactivation selectively disrupts the reconsolidation of the emotional component of the memory, leaving declarative memory of prior contingency learning intact. Indeed, it has also been found that propranolol administered so as to interfere with fear memory reconsolidation reduces subjective distress associated with the CS+ (Soeter & Kindt, 2012a), further indicating an impact at the emotional level.

In addition to demonstrating a Reactivation × Manipulation interaction and memory specificity, Kindt and Soeter (2018) also found evidence consistent with both a time-dependent effect of the propranolol manipulation, and a dissociation of immediate and delayed effects. Whereas previous studies administered oral propranolol 90 min before or immediately after memory reactivation, this study included conditions in which propranolol was administered to participants either immediately, 1 hr, or 2 hr after reactivation. Participants receiving propranolol immediately or 1 hr after, but not 2 hr after reactivation displayed the anticipated neutralization of the fear-potentiated startle response, thereby demonstrating that the interaction between reactivation and propranolol is dependent on the drug being administered within a specific time window. Given that propranolol takes 1 hr–2 hr to reach peak plasma levels (Gilman & Goodman, 1996), this would suggest that beta-adrenergic receptors are required for the reconsolidation of memory within a time period under 4-hr postreactivation. Furthermore, Kindt and Soeter (2018) found that participants retained a functional short-term memory (STM) trace after the intervention, with startle responses to the CS+ remaining potentiated even up to 12 hr after propranolol + reactivation, as long as they were tested on the same day of the intervention. Neutralization of fear memory expression was evident only once participants had slept, thus demonstrating not only a dissociation of short- and long-term effects, but also revealing a crucial role of sleep in the transformation of fear memory after the putative disruption of reconsolidation.

Not all studies using propranolol to interfere with the reconsolidation of fear memories have produced such effects, however. Two studies (Bos, Beckers, & Kindt, 2014; Schroyens, Beckers, & Kindt, 2017) failed to demonstrate the expected reduction in startle responding in the propranolol + reactivation group that was seen in previous studies. However, the results of these studies displayed a number of other anomalous features. Not only did propranolol fail to reduce conditioned startle responses, but startle and skin conductance also failed to display statistically significant evidence of extinction learning. Moreover, participants showed less robust differential fear conditioning on Day 1 and appeared to show less trust of the nonoccurrence of shock with the control stimulus (CS−) on subsequent testing days. Hence, these results might reflect a general uncertainty of participants in the experimental procedure that could have precluded the generation of clear associative learning and a subsequent prediction error (for further discussion of prediction error in reconsolidation).

Spring et al. (2015) reported a failure to reduce conditioned responding to stimuli with prereactivation propranolol in a modified conditioning paradigm designed to produce particularly strong fear memories. However, the only physiological measure used in this study was skin conductance, which was not affected by propranolol administered before or after reactivation in any of the aforementioned studies. Hence, a failure to reduce conditioned responding was predictable on the basis of existing findings. Moreover, that this paradigm generated particularly strong learning is questionable given the large proportion of participants that failed to acquire differential responding. In any case, the strength of a memory is not a clear boundary condition for the previously discussed effects, as propranolol has been found to reduce fear responding even in strong emotional memories. For example, Soeter and Kindt (2012b) administered yohimbine, an $\alpha_2$-adrenergic receptor antagonist that stimulates noradrenergic activity (Charney, Woods, Goodman, & Heninger, 1987), during acquisition of fear conditioning. Noradrenergic activation can facilitate long-term memory formation, and is also thought to partly explain the enhancement of memories formed during stress or trauma (Cahill, Prins, Weber, & McGaugh, 1994; Gazarini, Stern, Carobrez, & Bertoglio, 2013; Gelinas & Nguyen, 2005). The associative memories formed under the influence of yohimbine were harder to extinguish, and prompted fear generalization, indicating greater memory strength, yet could still be neutralized by the administration of propranolol after reactivation.

Both age and strength of memories have typically been viewed as boundary conditions of reconsolidation in animal research, with older or stronger memories becoming increasingly resistant to change (Eisenberg & Dudai, 2004; Elsey & Kindt, 2017a). However, it should be noted that boundary conditions are typically inferred from negative findings with a single reactivation procedure (Elsey & Kindt, 2017a; Milekic & Alberini, 2002), even though one would not expect a single, universally effective reactivation procedure that always triggers reconsolidation. Elsey and Kindt (2017a) have reviewed several potential means of overcoming the supposed boundary conditions of age and strength of memory on the induction of reconsolidation. For instance, old or strongly trained memories may be rendered labile by longer reactivation sessions (Frankland et al., 2006; Suzuki et al., 2004) or by exposure to novel stimuli during reactivation (Winters, Tucci, & DaCosta-Furtado, 2009). Furthermore, it has been observed in

animal models that strong memories can undergo reconsolidation if they are reactivated at remote time-points (Robinson & Franklin, 2010; Wang, de Oliveira Alvares, & Nader, 2009). Hence, it may be that clear-cut boundary conditions do not exist. This aligns with the postulated role of reconsolidation as an adaptive mechanism for keeping memories up-to-date (Lee, 2009). From this perspective, as long as the memory reactivation involves a discrepancy or a match-mismatch experience (i.e., a prediction error: Rescorla & Wagner, 1972) between what has already been learned and what is experienced, then reconsolidation may be triggered (Morris et al., 2006; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Sevenster, Beckers, & Kindt, 2012b; Sevenster, Beckers, & Kindt, 2013, 2014b; Wang & Morris, 2010).

In line with this conceptualization, Sevenster et al. (2013) found that an unexpected change in contingency, even if this meant that an aversive outcome that was not fully expected occurred upon reactivation (i.e., a shock did follow the presentation of the CS when training had suggested a lower reinforcement rate), was necessary for the memory disrupting effects of propranolol. Similarly, when there was no possibility of acquiring new information about the contingencies—such as when the US electrodes were not attached—propranolol had no effect after reactivation (Sevenster et al., 2012b). Finally, Sevenster et al. (2014b) found that the extent of prediction error determined the fate of memory after reactivation. In this study, a single prediction error rendered the memory susceptible to the disruptive effects of propranolol, whereas multiple prediction errors appeared to lead to a transitional state between reconsolidation and extinction, protecting the initially reactivated memory from propranolol-induced changes (referred to by Merlo, Milton, Goozée, Theobald, & Everitt, 2014—who observed a similar phenomenon in rats—as a "limbo" state). These findings parallel work in a range of animal models that indicate that prediction error may be necessary for the elicitation of reconsolidation (Alfei, Ferrer Monti, Molina, Bueno, & Urcelay, 2015; Fernández, Boccia, & Pedreira, 2016), and suggest that memory reconsolidation is only triggered when the retrieval experience contains novel or surprising information. Furthermore, they indicate that prediction error does not always elicit reconsolidation. With multiple prediction errors, extinction learning or a transitional "limbo" state are triggered. As these studies by Sevenster and colleagues (2012b, 2013, 2014b) were intended to determine the effects of specific types of reactivation, and because it had already been established that propranolol alone or reactivation alone do not result in neutralization of conditioned responses, controls for reactivation alone, or for propranolol alone, were not always included.

**Practical and clinical applications of pharmacological blockade of reconsolidation.** While a range of disorders can be seen to have maladaptive emotional memories as a core feature, the finding that propranolol—or other pharmacological agents—might interfere with the reconsolidation of emotional memories currently seems most relevant for the treatment of trauma- and anxiety-related disorders. Cases such as posttraumatic stress disorder (PTSD) and specific phobias are often resistant to typical psychotherapeutic and pharmacological interventions, which can involve costly and very time-consuming procedures (Durham, Higgins, Chambers, Swan, & Dow, 2012; Hofmann & Smits, 2008; Loerinc et al., 2015). The need for efficient and effective treatments is clear, and the translation of reconsolidation research from animal models, to human experiments, to clinical applications, may provide them (Elsey & Kindt, 2017b; Kindt, 2014). In fact, before experimental work in humans had been conducted on propranolol and reconsolidation, some researchers had already made the leap from animal research to clinical trials, with both promising and disappointing results.

Brunet et al. (2008) had patients with chronic PTSD recall their traumatic experiences so as to reactivate their maladaptive memories, and then gave them either propranolol or placebo (double-blind). One week later, participants' physiological responses to script-driven imagery (standardized, 30-s scripts about a traumatic event that were generated by talking with the patient about their trauma, which were then recorded and played back to the patient) were found to differ significantly between groups, with the propranolol group even scoring below previously delineated PTSD cutoffs in some cases. However, there was no control for the effects of propranolol without reactivation, precluding a clear demonstration of a Reactivation $\times$ Manipulation interaction. Similarly, Brunet et al. (2011) found that the administration of propranolol prior to weekly script-driven exposure sessions for PTSD produced a rapid reduction in PTSD symptoms; an effect that compared favorably to standard exposure sessions (though neither a placebo nor a reactivation control group were used in this study, and drugs were not administered blind). On the other hand, Wood et al. (2015) failed to find an effect of propranolol (as well as of glucocorticoid receptor antagonist mifepristone, or D-cycloserine + mifepristone) and reactivation on subsequent script-driven responding, though they noted some concerns in interpreting the data due to a lack of baseline assessments and possible floor effects (participants generally did not display as much physiological arousal as in previous studies and reported mild to moderate PTSD).

Though we can only speculate at this stage, it is possible that insights gained from experimental studies could improve the strength and consistency of such reconsolidation-based interventions (Elsey & Kindt, 2017a, 2017b). Script-driven imagery or lengthy script preparation sessions may reactivate the traumatic memory but not optimally elicit reconsolidation, given that they merely recapitulate the traumatic event. As has been discussed, prediction error appears to be very important for the destabilization of consolidated memories. With this in mind, it may be preferable to use an imagery rescripting approach to trauma reactivation, in which the original trauma is initially followed accurately to produce reactivation, but the hotspot of the trauma—the point at which emotional distress reaches its peak—is changed to provide the patient with more of a mismatch experience. Such single sessions have produced positive results in a series of PTSD cases (three out of four patients significantly benefitted; Kindt & van Emmerik, 2016). Though promising, such results require support in placebo-controlled studies that also rule out alternative explanations. Currently, trials of these reconsolidation-based interventions in PTSD present a mixed picture.

Beyond PTSD, it has also been found that the pharmacological blockade of reconsolidation could prove effective in the treatment of specific fears and phobias. In a randomized, double-blind, placebo controlled study in participants with high fear of spiders, Soeter and Kindt (2015a) found that the administration of propranolol immediately after a brief exposure to a tarantula produced a dramatic drop in fear of spiders. After the intervention, participants

in the active treatment condition were able to touch or even have a spider walk over their hands. In contrast, the placebo group, and a group that had received propranolol in the absence of reactivation, showed no improvement relative to pretreatment. Participants' negative cognitions about spiders did not immediately change in line with their behavioral and emotional transformations, but had dropped significantly below a phobia cutoff score 3 months after the treatment. These treatment effects were maintained at least up until one year after treatment, at which point there was still no change in the behavior or questionnaire responses of participants in the inactive experimental conditions. This study did not include a control group that received neither reactivation nor propranolol, though it should be noted that the participants had retained their fear of spiders over many years, without propranolol and often with periods where reactivation did not occur. It is reasonable to assume that such a condition would not result in significant changes in fear of spiders. Case studies of similarly successful treatments for other phobias have also been reported (e.g., mice in Elsey & Kindt, 2017a), though such single cases are unable to provide evidence for the suggested reconsolidation criteria.

Outside of anxiety-related research, animal studies have provided evidence that propranolol may also be a tool for the disruption of addiction- or reward-related memory reconsolidation (Bernardi, Lattal, & Berger, 2006; Diergaarde, Schoffelmeer, & De Vries, 2006; Fricks-Gleason & Marshall, 2008; Milton, Lee, & Everitt, 2008; Otis & Mueller, 2011; Robinson & Franklin, 2010; Xue et al., 2017). There is conflicting evidence regarding the efficacy of such an approach to the treatment of addiction in humans. Saladin et al. (2013) found that propranolol (double-blind, placebo controlled) administered after a brief exposure to video and *in vivo* cocaine cues produced a greater decrease in cocaine craving at follow-up than in the placebo condition among cocaine dependent individuals. Lonergan et al. (2016) found that six script-driven reactivation + propranolol sessions significantly reduced craving, relative to reactivation + placebo, in individuals with a range of different substance addictions. However, in another study of cocaine craving, Jobes et al. (2015) found that propranolol administered 120 min before cocaine cue exposure (involving a personalized script, tactile cues, and cocaine-related images) actually increased cocaine cue reactivity at test relative to placebo.

Possible reasons for these conflicting findings are worth considering and are open to testing. Saladin et al.'s (2013) study used a larger sample size and focused on cocaine dependent individuals, whereas those in Jobes et al. (2015) were actually patients on methadone maintenance for recovery from heroin who also used cocaine. It is not known how these factors might affect the results. In addition, the timing of drug administration in Jobes et al. (2015) seems less appropriate than the administration of propranolol a shorter time before or indeed immediately after cue exposure. It is also likely that the parameters of the reactivation session itself are of importance. Experimental studies suggest that an optimal session might consist of a prediction error, and that its length should not elicit extinction. Further animal research and human studies with carefully timed administration of drugs and manipulation of the reactivation session could be used to delineate the optimal times for drug delivery and session length. Experimental work has looked at this (e.g., Alfei et al., 2015; Kindt & Soeter, 2018; Merlo, Milton, Goozée, Theobald, & Everitt, 2014), but the translation to clinical populations is particularly difficult and worth investigating.

One final consideration is that reactivating addiction memories using cues associated with drug taking may not be as effective as using the actual drug as a means of reactivation. Pachas et al. (2015) reactivated memories for smoking by having participants write about a typical smoking experience, and failed to find any effect of propranolol + reactivation on later physiological reactivity to script driven imagery for smoking. In contrast, Xue et al. (2017) found that propranolol (vs. placebo) given 1 hr before (vs. 6 hr after) partially smoking a cigarette led to reduced preferences for nicotine-related conditioned stimuli and less craving after presentation of such cues or priming with nicotine. As this study only included a comparison of reactivation + propranolol inside versus outside the reconsolidation window, it could not fully establish a Reactivation × Manipulation interaction. However, the reactivation + delayed propranolol group might be seen as controlling for nonspecific effects of both reactivation and propranolol, thus indicating an interaction. The use of such a condition also provides a demonstration of time dependency of the effect of propranolol. The contrasting findings of Pachas et al. (2015) and Xue et al. (2017) highlight that a lack of an intervention effect does not rule out that a reconsolidation-based approach could be effective if different means of memory reactivation are attempted (Elsey & Kindt, 2017a). This should be kept in mind when evaluating null results for clinical interventions in particular, where researchers are only beginning to scratch the surface of the optimal means of reactivation.

**Alternative explanations.** Although the amnestic effects of beta-adrenergic blockade after memory reactivation are relatively consistent and convincing, the efficacy of a treatment or experimental intervention does not necessarily provide proof of the proposed mechanisms or theory underpinning it. It is likely that effective treatments derived from reconsolidation-based research will ultimately require a firm understanding of the precise mechanisms of action. Without understanding why a treatment works, clinicians may place undue emphasis on aspects of the intervention that are unnecessary or even counterproductive for generating the desired outcome, leading to inefficiency and inefficacy. Poorly understood interventions may also be proposed for cases that would not be expected to benefit given the working mechanisms of the treatment. In addition, where particular drugs are thought to be required, people may be unnecessarily excluded from treatment due to contraindications that would not apply if equally effective alternatives could be used instead. Therefore, alternative explanations to reconsolidation accounts should be assessed.

One alternative to reconsolidation is that propranolol administered before reactivation (as in some studies mentioned above) might have interfered with memory retrieval. This alternative explanation has been effectively refuted. Differential responses to the CS+ and CS− are observed at reactivation regardless of whether propranolol was administered before or afterward, suggesting intact retrieval. Most importantly, propranolol administered after reactivation displays the same amnestic effects (Sevenster et al., 2013, 2014b; Soeter & Kindt, 2012a, 2015b). It is also clear that the memory-modifying effects of propranolol are not attributable to general anxiolytic or dampening effects of propranolol, given that they are specific to the reactivated memory and depend upon a specific type of reactivation (Sevenster et al., 2013;

Soeter & Kindt, 2011, 2012b). Enhanced extinction learning is also implausible, as it has been shown that even when reactivation is reinforced, which would preclude extinction, the neutralization of startle responses can still occur provided that the reactivation includes a prediction error (Sevenster et al., 2013).

However, based on early research into retrieval-induced retrograde amnesia in animals (Bradley & Galal, 1988) and more recent findings (Gisquet-Verrier et al., 2015), a modified state-dependent retrieval (MSDR) account has been proposed as an alternative to the idea of disrupted reconsolidation typically used to explain amnesia in animal models. This account could apply to the blockade of reconsolidation with beta-adrenergic agents in humans, as discussed below.

Similarly to reconsolidation-based explanations, the MSDR account of amnestic effects suggests that memories can incorporate new information upon reactivation. However, proponents of MSDR suggest that protein synthesis may not in fact be required in a process of memory restorage. Rather, the internal state induced by protein synthesis inhibitors such as anisomycin (as well as a host of other amnestic agents, including propranolol) can be incorporated into a memory, thereby becoming an important retrieval cue, or "occasion setter," for successful memory recovery (Riccio et al., 2006). In support of this, some animal studies have demonstrated that the administration of a protein synthesis inhibitor before testing can recover memories previously thought to have been lost by protein synthesis inhibition (Gisquet-Verrier et al., 2015). Hence, it appears that such memories have become state dependent and merely fail to be retrieved due to lack of sufficient retrieval cues, rather than having had their reconsolidation disrupted. The delayed onset of amnesia is explained in this model because shortly after an amnestic intervention, the amnestic agent is still present or has only recently passed, thus aiding retrieval. If an internal state induced by propranolol is incorporated into the memory and becomes a crucial retrieval cue, this could explain the amnesia observed in human subjects.

Such an explanation could prove important for human studies because it suggests that a wide range of drugs or other interventions that produce an altered state might be used to modify memory accessibility, potentially allowing people with contraindications to particular drugs to benefit from memory modifying treatments. Of course, these findings could also have implications for the anticipated long-term outcomes of such treatments if sufficient triggers would be expected to produce memory retrieval.

There are, however, a number of limitations to the MSDR account. First, not all drugs that induce an internal state lead to later amnesia, and it is unclear from a MSDR account why this should be so. Peripherally acting beta-blockers, such as nadolol, do not have the same amnestic effects as centrally acting beta-blockers, despite producing similar states (Gazarini et al., 2013; Kindt & Soeter, 2018; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998). However, it might be argued that the states induced by centrally and peripherally acting betablockers are indeed experienced differently, or that the internal state induced must be one derived from a centrally acting drug.

Studies utilizing two drugs (one to either facilitate or block the hypothesized destabilization of memory, and the other to disrupt restabilization) also provide a challenge to an MSDR account. If reactivation + anisomycin is preceded by ifenprodil administration (which is thought to prevent memory destabilization by blocking NMDA receptors), then amnesia is not observed (Ben Mamou, Gamache, & Nader, 2006). In cases where memories are particularly strong and resistant to disruption via reconsolidation (e.g., after stress), then prereactivation administration of D-cycloserine (DCS, thought to facilitate the induction of reconsolidation through agonistic effects at NMDA receptors) renders the memory vulnerable to disruption (Bustos, Giachero, Maldonado, & Molina, 2010). In a similar vein, if amnesia is simply due to lack of drug-state retrieval cues rather than specific effects of drugs on the neurobiological process of reconsolidation, it is unclear why certain drugs, such as yohimbine, strengthen a memory when administered after reactivation, even though testing occurs in a drug free state (Gazarini et al., 2013).

MSDR also struggles to explain why amnestic treatments have an effect only after specific types of reactivation. For example, DCS alone increases the later expression of memory when reactivation is brief, consistent with enhanced reconsolidation strengthening the memory, but reduces later memory expression when reactivation is longer, consistent with enhanced extinction learning (Lee, Milton, & Everitt, 2006). As noted earlier, prediction error appears to be necessary for amnestic effects to be observed in some paradigms such as fear conditioning, yet a drug induced internal state and memory reactivation occur regardless of prediction error. Finally, Kindt and Soeter (2018) found that amnestic effects of propranolol were observed 12 hr after the intervention, but crucially only after a night of sleep. One would expect drug levels in the brain to be similar after 12 hr with or without sleep, and so propranolol ought to function equally as a retrieval cue in both these conditions—either resulting in amnesia in both the sleep and no sleep groups if the drug is washed out, or producing retrieval in both if the drug is still present. The neutralization of fear-potentiated startle only in the sleep group refutes this.

Such findings can be readily understood within the framework of reconsolidation, but the MSDR account does not specify why only certain drugs, or combinations thereof, would have such divergent effects, or why particular types of reactivation are necessary. An MSDR account incorporating such findings would need to grant that there are specific neurobiological processes—brought about by specific means of reactivation—that render a memory malleable (i.e., destabilization) for a specific time (i.e., a labile or unstable period), and would differ from reconsolidation only with respect to the idea that some sort of restabilization process is required in order for the memory to persist. What, from an MSDR perspective, closes off this period of memory malleability, given that time since reactivation is only relevant insofar as it corresponds to particular processes that change with it (such as restabilization, from a reconsolidation perspective)?

Although several findings are difficult to explain under a MSDR account (see also Nader, 2015), the ultimate test for a MSDR account is the reintroduction of the amnestic agent prior to testing the memory, which has not been conducted in controlled tests in a human sample. We have not observed the return of fear with the repeated administration of propranolol in previously phobic participants in our lab, but this has not been assessed in multiple subjects and with the number of different conditions necessary to definitively refute such an explanation. Such alternative hypotheses will remain open until directly tested.

**Summary of pharmacological blockade of reconsolidation.** Table 2 provides an overview of studies of the pharmacological

Table 2
*Reviewed Studies of Pharmacological Interventions in Aversive and Appetitive Memory*

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Bos, Beckers, & Kindt, 2014 | Pavlovian conditioning | Propranolol (40 mg) | 90 min before reactivation | No | — | — | — | Propranolol + reactivation failed to neutralize FPS. |
| Brunet et al., 2008 | PTSD | Propranolol (40 mg SA + 60 mg LA) | Shortly after reactivation + LA dose 2hrs later | — | — | — | — | Propranolol + reactivation reduced responsivity to script-driven imagery versus placebo + reactivation. No control for effects of propranolol without reactivation. |
| Brunet et al., 2011 | PTSD | Propranolol (doses typically 40 mg SA + 60 mg or 80 mg LA) | Typically SA dose 90 min before reactivation + LA dose shortly after reactivation | — | — | — | — | Study included three open label trials, with multiple sessions of reactivation + propranolol, with no placebo control or propranolol only control. PTSD symptomatology improved significantly over study period. |
| Jobes et al., 2015 | Cue reactivity to cocaine in polydrug users | Propranolol (40 mg) | 120 min before reactivation | No | — | — | — | Propranolol + reactivation group showed greater drug cue reactivity than placebo + reactivation during reactivation − the opposite effect to that expected − with a trend towards heightened reactivity when assessed at 1 week and 5 weeks |
| Kindt & Soeter, 2018 | Pavlovian conditioning | Propranolol (40mg) | 1 hr before, immediately after, 1 hr after, 2 hr after | Yes* | Yes | Yes | Yes | Propranolol administered less than 2 hr after reactivation neutralized FPS to the reactivated memory. Effect was observed only at delayed testing after sleep. Used a within subjects control for reactivation versus no reactivation. |
| Kindt & van Emmerik, 2016 | PTSD | Propranolol (40mg) | Shortly after reactivation | — | — | — | — | Case series of four patients without placebo control or test of nonspecific effects of propranolol. Three of the patients significantly benefitted. |
| Kindt, Soeter, & Vervliet, 2009 | Pavlovian conditioning | Propranolol (40 mg) | 90 min before reactivation | Yes* | — | — | — | Propranolol + reactivation (vs. placebo + reactivation or propranolol only) neutralized FPS but not declarative memory for contingencies. Did not include control for no reactivation + no propranolol, but FPS is maintained when nothing is done to the memory between learning and test. |

(*table continues*)

Table 2 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Lonergan et al., 2016 | Cue reactivity in cocaine addiction | Propranolol (1 mg/kg) | 60 min before reactivation | — | — | — | — | Propranolol + reactivation group had reduced craving relative to baseline at Session 6, whereas placebo group did not. No control for nonspecific effects of propranolol. |
| Pachas et al., 2015 | Cue reactivity in nicotine addiction | Propranolol (40 mg–80 mg SA and 60–120 LA) | SA propranolol 90 min before reactivation + LA propranolol immediately before reactivation | No | — | — | — | Propranolol + reactivation had no benefit relative to placebo + reactivation on responsivity to script-driven drug imagery. |
| Saladin et al., 2013 | Cue reactivity in cocaine addiction | Propranolol (40 mg) | Shortly after reactivation | — | — | — | — | Propranolol + reactivation group had lower cocaine cue reactivity than placebo + reactivation group the day after treatment, but not at 1-week follow-up. Both groups had lower cue induced craving than before treatment, and no differences in cocaine use were observed. No control for nonspecific effects of propranolol. |
| Schroyens, Beckers, & Kindt, 2017 | Pavlovian conditioning | Propranolol (40 mg) | Immediately after reactivation | No | — | No effect | — | Reactivation followed by propranolol failed to neutralize FPS. |
| Sevenster, Beckers, & Kindt, 2012b | Pavlovian conditioning | Propranolol (40 mg) | 90 min before reactivation | RTD | — | — | — | Placebo-controlled study demonstrating that a specific type of reactivation (with shock electrodes attached, allowing for prediction error) was necessary for propranolol to neutralize FPS. |
| Sevenster, Beckers, & Kindt, 2013 | Pavlovian conditioning | Propranolol (40 mg) | Immediately after reactivation | RTD | — | — | — | Propranolol + reactivation involving prediction error neutralized FPS. Did not include a placebo control, but dependence on type of reactivation suggests neutralization is not a nonspecific effect of propranolol. |
| Sevenster, Beckers, & Kindt, 2014b | Pavlovian conditioning | Propranolol (40 mg) | Immediately after reactivation | RTD | — | — | — | Propranolol + reactivation with a single (but not multiple) prediction error neutralized FPS. Did not include placebo control, but dependence on type of reactivation suggests neutralization is not a nonspecific effect of propranolol. |

(*table continues*)

Table 2 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Soeter & Kindt, 2010 | Pavlovian conditioning | Propranolol (40 mg) | 90 min before reactivation | Yes* | — | — | — | Propranolol + reactivation neutralized FPS but not SCR or declarative memory for contingencies. Results were maintained at 1-month follow-up. Did not include control for no reactivation + no propranolol, but FPS is maintained when nothing is done to the memory between learning and test. |
| Soeter & Kindt, 2011 | Pavlovian conditioning | Propranolol (40 mg) | 90 min before reactivation | Yes* | — | Yes | — | Propranolol selectively neutralized FPS, specifically for the reactivated memory. Propranolol + reactivation participants did not display rapid reacquisition, and the effect generalized to category-related items. Used a within subjects control for reactivation vs. no reactivation. |
| Soeter & Kindt, 2012a | Pavlovian conditioning | Propranolol (40 mg) | Immediately after reactivation | — | — | — | — | Propranolol + reactivation neutralized FPS and subjective distress responses to the CS. Memory impairment was resistant to renewal. Study did not include a control for reactivation vs. no reactivation, precluding interpretation of an interaction (though previous studies clearly indicate an interaction effect). |
| Soeter & Kindt, 2012b | Pavlovian conditioning | Propranolol (40 mg) | 90 min before or immediately after reactivation | Yes* | — | Yes | — | Used yohimbine during learning to strengthen memory. Propranolol selectively neutralized FPS to the reactivated memory. Effects were resistant to reinstatement and generalized to related stimuli. Used a within subjects control for reactivation versus no reactivation. |

(*table continues*)

Table 2 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Soeter & Kindt, 2015a | Subclinical arachnophobia | Propranolol (40 mg) | Shortly after reactivation | Yes* | — | — | — | Propranolol + reactivation resulted in large drop in fear responses and increased approach behavior to spiders. Results were maintained at 1-year follow-up. No control for no reactivation + no propranolol, though fear was already long-lasting, and maintained in the control groups over the whole study period. |
| Soeter & Kindt, 2015b | Pavlovian conditioning | Propranolol (40 mg) | Immediately after reactivation | RTD | — | — | — | Propranolol after memory reactivation using an abstract representation of the CS neutralized FPS to the reactivated memory. No effects were observed when reactivation stimulus did not make clear which learned association was being reactivated. Used a within subjects control for reactivation without a placebo control. |
| Spring et al., 2015 | Modified Pavlovian conditioning | Propranolol (40mg) | 90 min before reactivation | ~No | — | No effect | — | Propranolol + reactivation failed to neutralize SCR responses. SCR is an outcome measure that has been shown to be insensitive to reactivation + propranolol in previous studies. |
| Wood et al., 2015 | PTSD | Study 1: Propranolol; Study 2: 1,800 mg Mifepristone; Study 3: 100 mg DCS + 1,800 mg mifepristone | Study 1: Propranolol before and after reactivation, or without reactivation; Study 2: Mifepristone before reactivation, or without reactivation; Study 3: DCS and mifepristone before reactivation | No | — | — | — | Included three studies with different drugs. Subjects receiving placebo + reactivation also served as controls for nonspecific drug effects in Experiments 1 and 2, receiving the drugs at the intake session without reactivation. Significant differences in physiological reactivity or PTSD symptomatology between active and inactive groups were not observed. |

(*table continues*)

Table 2 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Xue et al., 2017 | Cue reactivity in nicotine addiction | Propranolol (40 mg) | 60 min before or 6 hr after reactivation | Yes* | Yes | — | — | Participants receiving propranolol within the reconsolidation window had lower cue-induced craving than those receiving propranolol outside the window, and were also lower than the placebo + reactivation group. There were no reactivation only, propranolol only, or no reactivation + no propranolol control groups. Reactivation + delayed propranolol may be seen to control for nonspecific effects of reactivation and of propranolol, supporting an interaction. |

*Note.* 1 = Reactivation × Manipulation interaction; 2 = Time dependency; 3 = Memory specificity; 4 = Dissociation of immediate and delayed effects; — = not assessed; RTD = effects were dependent upon the type of reactivation; No effect = procedures were put in place to test a criterion, but the absence of any effect of the intervention negated their use (e.g., time dependency cannot be assessed if the intervention has no effect regardless of time). DCS = D-cycloserine; FPS = fear potentiated startle; LA = long acting dose; SA = short acting dose; SCR = skin conductance response; CS = conditioned stimulus.
~ Represents that a criterion may have been imperfectly demonstrated, or that the interpretation of this demonstration as being consistent with reconsolidation is uncertain (e.g., if observed memory impairments rapidly recover). Reasons are discussed in the summary column and in the main text. * Represents that we believe there is sufficient ground to infer a Reactivation × Manipulation interaction in a study, but that a strict 2 × 2 ANOVA with a test for an interaction was not conducted.

blockade of reconsolidation in aversive and appetitive memories. In summary, experimental and clinical work has demonstrated quite potent effects of propranolol administered so as to disrupt a putative process of reconsolidation. In several human fear-conditioning studies using the standard 3-day design of reconsolidation-based interventions, findings have paralleled those used in animal models as evidence of reconsolidation: several studies indicate an interaction between memory reactivation and propranolol administration, and that the impact of propranolol is specific to the reactivated memory trace. Moreover, two studies have demonstrated that such effects are only observed when propranolol is administered within a specific time window after reactivation (Kindt & Soeter, 2018; Xue et al., 2017), and there is also evidence for the dissociation of immediate and delayed effects (Kindt & Soeter, 2018). Of further interest, as has been demonstrated in some animal models of reconsolidation, characteristics of the reactivation session, such as prediction error, seem to determine whether reconsolidation-like effects are observed in studies of fear conditioning (Sevenster et al., 2013, 2014b). A small meta-analysis of studies in which propranolol was given in conjunction with memory reactivation, comprising eight studies, suggested a medium effect size of the intervention (Hedge's g = 0.56; Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013).

The use of propranolol to disrupt the putative process of memory reconsolidation has demonstrated some clinical utility, yet it is also clear that more research is needed to convincingly demonstrate the clinical efficacy of such an approach. Studies have often not included appropriate controls, or have been conducted with very small sample sizes. Properly powered, randomized controlled trials will be necessary for demonstrating the value of such a reconsolidation-based approach, but it should be stressed that premature attempts at running such trials may lead to false negatives: Abundant evidence suggests that reconsolidation-like effects rely on particular reactivation conditions that can be highly complex even in simple laboratory models, and there are many difficult steps in the translation of experimental findings to clinical applications (Elsey & Kindt, 2017a, 2017b). Hence, greater attention should be paid to the necessary and sufficient conditions for inducing such effects across the range of maladaptive memories met with in clinical practice. Finally, reasons for failed replications in clinical and experimental studies, as well as alternative explanations for reconsolidation-like effects, could be further investigated.

## Retrieval-Extinction Procedures for Aversive and Appetitive Memories

**Experimental studies.** Translational approaches using fear conditioning as an experimental model of fear and anxiety have also proven useful in nonpharmacological reconsolidation-based interventions. Drawing upon the idea that memory reconsolidation serves as a means of incorporating new information into memories and thus maintaining the relevance of memory traces under changing environmental conditions (Lee, 2009), it has been suggested that extinction training after a brief reactivation of memory might result in the incorporation of extinction learning directly into the reactivated memory trace. This is known as a "retrieval-extinction" procedure. As noted above, it is now widely believed that the

reduction of fear resulting from standard extinction reflects the generation of a new inhibitory memory trace, rather than a rewriting of the original memory (Bouton, 2002). This explains why the original memory is often seen to resurface with a change of context (renewal), exposure to the unconditioned stimulus (reinstatement), or simply after the passage of time (spontaneous recovery; Bouton, 2002). If the original memory trace were to be updated, then this could produce substantial benefits beyond standard extinction training.

To assess this possibility, Monfils, Cowansage, Klann, and LeDoux (2009) conducted a study in rodents and found that extinction training shortly but not 6 hr or 24 hr after a brief reactivation trial led to a more persistent attenuation of fear responses than extinction alone. Rodents that underwent a retrieval-extinction procedure showed lower levels of reinstatement, renewal, and spontaneous recovery, than those undergoing standard extinction. Subsequently, Schiller et al. (2010) extended these findings in a human fear-conditioning study, using geometric shapes as the CSs and electric shocks as the USs. Similarly to Monfils et al. (2009), the skin conductance responses of participants who received extinction training 10 min (but not 6 hr) after a single unreinforced exposure to the CS+ showed reduced levels of spontaneous recovery relative to standard extinction. This attenuation was specific to the reactivated memory. Moreover, these group differences were sustained in those participants who returned to the lab for a reinstatement test approximately 1 year later.

Thus, Schiller et al. (2010) demonstrated both memory specificity and time dependency of the postreactivation intervention. Strictly, a Reactivation × Manipulation interaction was not demonstrated, as the study was missing both a reactivation only condition, and a control for no reactivation and no extinction. However, it is evident from a wealth of other studies that a single retrieval of a conditioned response does not prevent spontaneous recovery or reinstatement, and that in the absence of reactivation or retrieval, memory can persist over the time periods used in Schiller et al. (2010). It might also be argued that conducting extinction training outside the putative reconsolidation window functions as a test of nonspecific/additive effects of both reactivation and extinction.

Steinfurth et al. (2014) extended these results by demonstrating that such effects could be observed when memories were reactivated 1 week after learning, as well as after a delay of 1 day, as in Schiller et al. (2010). Other researchers have extended these findings by showing that retrieval-extinction procedures can reduce fear memory recovery relative to standard extinction using an aversive sound as a US, rather than an electric shock (Johnson & Casey, 2015; Oyarzún et al., 2012).

Subsequently, an interesting variation on retrieval-extinction procedures was presented, in which a weaker version of the US, rather than the CS+, was used to reactivate conditioned responses before extinction (Liu et al., 2014). This procedure also resulted in an attenuation of fear responses beyond that achieved by standard extinction. Moreover, the responses to multiple CSs associated with the US could be affected using this procedure, which may prove important for clinical interventions, in which a wide range of stimuli might have become linked to a traumatic event. This study also found evidence consistent with time dependency of the manipulation, though with a suboptimal delay between retrieval and extinction of 24 hr, as opposed to extinction on the same day as reactivation but outside the reconsolidation window.

Behavioral and peripheral physiological measures during retrieval-extinction have since been supplemented in independent samples with measures of blood oxygenation level dependent (BOLD) activation—a surrogate signal for neural activity. Agren, Engman, et al. (2012) found that extinction within the reconsolidation window (relative to 6 hr after reactivation) led to reduced activity in the basolateral amygdala when return of fear was tested. Functional connectivity between the amygdala and the insula, hippocampus, and midline anterior cingulate were greater in the 6-hr group, suggesting that connectivity with other brain regions, as well as activation in the amygdala itself, is affected by retrieval-extinction. This study did not include an extinction only, reactivation only, or no reactivation + no extinction group, although again it may be argued that conducting reactivation with extinction outside the reconsolidation window functions as a test of nonspecific effects of both combined. Schiller, Kanen, LeDoux, Monfils, and Phelps (2013), found that the ventromedial prefrontal cortex (vmPFC)—a region believed to be involved in extinction learning (Phelps, Delgado, Nearing, & LeDoux, 2004)—was more strongly engaged during standard extinction than retrieval-extinction. Connectivity between the vmPFC and amygdala during early extinction was also greater for the nonreminded CS+ than the retrieval-extinction CS+, perhaps reflecting a difference in the fear-reduction process that was occurring. Hence, just as animal studies have indicated that reconsolidation and extinction may have different neurobiological signatures (Merlo et al., 2014; Suzuki et al., 2004), these findings hint that neural activity in humans undergoing modified extinction procedures could also differ from standard extinction.

However, a subsequent study using a much larger sample (with a final analysis using 70 participants, rather than 19 as in Schiller et al., 2013, and 22 in Agren, Engman, et al., 2012) failed to support these findings (Klucken et al., 2016). Klucken et al. (2016) found no evidence for BOLD-response differences between retrieval-extinction and standard extinction in the amygdala or vmPFC during extinction, reinstatement, or reextinction. Only when using more liberal statistical procedures could any differences between groups be observed, and these were in different regions to those indicated by Agren, Engman, et al. (2012) and Schiller et al. (2013).

Some other behavioral studies have also failed to find support for the idea that a retrieval trial prior to extinction significantly attenuates later fear responding. In two independent samples, Soeter and Kindt (2011) and Kindt and Soeter (2013) found that extinction within the reconsolidation window did not prevent the recovery of fear responses to fear-relevant conditioned stimuli (stimuli that are argued to have posed a threat to survival to ancestral humans, such as snakes; Seligman, 1971) using both startle and skin conductance as physiological measures. Other studies have also failed to find advantages of retrieval-extinction relative to standard extinction using fear-relevant stimuli (Fricchione et al., 2016; Meir Drexler et al., 2014). Golkar, Bellander, Olsson, and Öhman (2012) found that a retrieval-extinction procedure failed to prevent the return of fear for both fear-relevant and fear-irrelevant stimuli (stimuli with no specific relevance to human evolution and survival, such as geometric shapes). Similarly, Warren et al. (2014) did not observe consistent effects of retrieval

extinction in a study assessing whether online expectancy ratings might also affect retrieval-extinction outcomes. Participants in all groups displayed spontaneous recovery at test, and in retrieval-extinction groups this did not appear to depend on whether the memory was reactivated or not. Though there may be differences in susceptibility to retrieval-extinction effects as a function of genotype (Agren, Furmark, Eriksson, & Fredrikson, 2012; Asthana et al., 2016; Klucken et al., 2016), this seems an unlikely explanation for divergent findings across research groups, unless there is reason to assume systematic differences in the genetic make-up of the participants.

Data from studies of retrieval-extinction procedures were subjected to a meta-analysis, comprising data from 310 human subjects (Kredlow, Unger, & Otto, 2016). Kredlow et al. (2016) concluded that retrieval-extinction had a small-to-moderate effect for preventing recovery of fear responses relative to standard extinction. Though these effects were not moderated by age or gender, a potentially clinically relevant moderator was discovered. Specifically, it was found that whereas the effect was moderate-to-large with fear-irrelevant stimuli, effects were near zero when fear-relevant stimuli were used. While there are cases of phobias for all kinds of totally innocuous stimuli, and neutral cues can function as reminders for trauma in PTSD, the overwhelming majority of anxiety disorders involve fear-relevant stimuli (Mineka & Öhman, 2002; Seligman, 1971). This could prove a stumbling block for the use of retrieval-extinction procedures in clinical practice. However, Thompson and Lipp (2017) found that skin conductance responses to both fear-relevant and fear-irrelevant conditioned stimuli could be eliminated using a retrieval-extinction procedure with the US as a means of reactivation. Clinical trials of retrieval-extinction procedures will be the ultimate test of their utility in the treatment of anxiety disorders, and currently do not provide convincing evidence for or against this prospect.

**Practical and clinical applications of retrieval-extinction procedures.** Although retrieval-extinction procedures have been relatively extensively studied in fear-conditioning paradigms in humans, only a handful of studies have assessed whether retrieval-extinction procedures are more efficacious than standard extinction protocols in individuals with anxiety- or trauma-related disorders. Shiban, Brütting, Pauli, and Mühlberger (2015) had two clinically phobic groups undergo virtual reality (VR) exposure therapy for fear of spiders. One group received a brief VR reactivation session with spiders, whereas the other received a neutral VR reactivation with a plant, before exposure. Both groups significantly benefitted from the treatment, but there were no differences between them, suggesting that the addition of a brief reactivation shortly before exposure did not add anything beyond standard VR exposure training. Similarly, Maples-Keller et al. (2017) randomized participants with fear of flying to receive a brief reactivation to either flying-related cues or neutral cues prior to each of four VR exposure sessions. The groups both benefitted significantly, but were not different from each other, though measures of heart rate and skin conductance suggested a possible advantage for those who received the brief exposure to flying-related cues.

Using a brief reactivation to a real-life spider or snake followed by *in vivo* exposure in spider and snake fearful individuals, Telch, York, Lancaster, and Monfils (2017) observed a trend toward lower peak fear levels when participants were exposed to their feared stimuli 1-month after treatment, and significantly less peak fear levels when tested using a generalization stimulus, relative to participants who underwent extinction training followed by a separate brief exposure. Hence, this study indicated that extinction-retrieval may have advantages over standard extinction, and also suggested the time dependency of effects, with the extinction-retrieval group displaying more fear at follow-up than the retrieval-extinction group. As in many previous studies, sufficient control groups were not used to clearly establish a Reactivation $\times$ Manipulation interaction, though it may be argued that the extinction-retrieval group functions as a control for both reactivation and extinction.

Given that spontaneous recovery was low even in standard extinction training in the above investigations, it is possible that additional benefits of modified extinction training were simply obscured, and it may still be that in more intractable cases variations on standard extinction will prove useful. Using larger sample sizes in future studies would help to more conclusively establish differences, or lack thereof, between retrieval-extinction procedures and other already effective interventions (standard extinction/exposure). A larger sample size in Telch et al. (2017) would have aided interpretation of how robust the effect of retrieval-extinction was, as group differences only just reached significance ($p = .04$), and analyses were conducted with the imputation of data for four participants in a small sample size ($N = 32$).

Björkstrand et al. (2016) found that a retrieval-extinction procedure using spider pictures attenuated basolateral amygdala reactivity to such pictures, and facilitated viewing of spider pictures, in a group of arachnophobic individuals. These findings were supported when participants were followed up 6 months later (Björkstrand et al., 2017). Hence, there is evidence that retrieval-extinction procedures might produce greater benefits than standard extinction in phobic individuals, but it would be most interesting to see such effects in actual behavior toward real spiders. In any case, these attempts at clinical translation highlight a positive aspect of retrieval-extinction procedures, which is that even if this approach does not lead to improvement beyond what is achieved with standard extinction, participants nevertheless receive exposure training and are able to experience the benefits it can provide.

With regards to appetitive memory, Xue et al. (2012) first demonstrated that a retrieval-extinction procedure could attenuate reinstatement of morphine conditioned place preference in rats. Translating these findings to humans, they found evidence for increased efficacy of a retrieval-extinction procedure in attenuating heroin cue-induced craving among abstinent heroin addicts, relative to extinction conducted outside of the reconsolidation window. After a baseline assessment of cue-induced craving, participants were assigned to undergo a 5-min heroin-related video reactivation session, followed 10 min or 6 hr later by an hour long extinction training session using a range of heroin cues (e.g., videos of drug use, exposure to heroin-related equipment). A further group was assigned to a neutral reactivation video condition, followed 10 min later by extinction training. When participants were assessed 1-day, 30-days, and 180-days posttreatment, participants in the group that had received a brief heroin cue reactivation followed shortly after by extinction training displayed significantly lower cue-induced craving than the neutral reactivation group and the group that had received extinction training

outside the reconsolidation window following reactivation. These results suggest time dependency of the manipulation in a clinical intervention. Xue et al. (2012) suggested that their findings might reflect a combination of reconsolidation disruption and enhanced extinction learning. Similarly, Germeroth et al. (2017) found that a retrieval-extinction procedure in a sample of smokers with intent to quit/reduce smoking attenuated cue-induced craving and reduced the number of cigarettes smoked per day relative to standard extinction, as assessed 2-weeks and then 1-month posttreatment. Physiological responses to smoking cues, urine cotinine levels, days abstinent and relapse were not different between groups.

Some researchers have expressed concern that a retrieval-extinction procedure for addiction might exacerbate reinstatement when those undergoing it are exposed to the rewarding properties of a drug again outside of the treatment context (Hutton-Bedbrook & McNally, 2013, see Alternative Explanations section below). Nevertheless, these findings are very promising, and convey the possible utility of retrieval-extinction procedures in disorders that do not respond well to standard extinction training. The development of translational paradigms for appetitive learning in humans that are responsive to retrieval-extinction and other reconsolidation-based approaches could significantly aid the development of clinical applications in cases such as drug addiction (the work of Xue et al., 2017 is positive in this respect). Appetitive memory has received relatively little attention in human reconsolidation-based research, yet the meta-analysis of Kredlow et al. (2016) found that appetitive memories in animals were more consistently susceptible to retrieval-extinction procedures than were aversive ones, which actually failed to show significant attenuation as a result of retrieval-extinction procedures overall.

**Alternative explanations.** As noted by Hutton-Bedbrook and McNally (2013), it may be argued that a prediction of the idea that extinction after a brief retrieval results in an updating of the memory trace, or an "unlearning" of the original memory while in an unstable state, is that such a procedure ought to return the human or animal undergoing it to an essentially naïve state. Research in both humans and animals suggests that this is not the case. In a rodent study of alcohol seeking, Millan, Milligan-Saville, and McNally (2013) found that animals that had never been trained to seek alcohol responded differently on initial acquisition than those that had received a retrieval-extinction manipulation when undergoing reacquisition. Likewise, Shumake and Monfils (2015) found that when fear memory was assessed using suppression of reward seeking, rather than freezing, rats that had received retrieval-extinction training did not display resistance to reinstatement. Similarly, in a test of memory savings after retrieval extinction, Monfils et al. (2009) found that retrieval-extinction actually slowed the reacquisition of fear responding when the conditioned stimulus was reinforced again, relative to naïve rodents, indicating that these animals had not simply had their memories erased.

However, it is questionable whether such findings refute the idea that some kind of memory updating process could be occurring. A memory might be partially updated or modified, rather than completely erased or unlearned. This could still confer benefits beyond standard extinction, but not be equivalent to the induction of a blank slate. As suggested by Clem and Schiller (2016), it is also possible that a combination of new learning and unlearning processes occur during retrieval-extinction. These authors further note that neurobiological markers that are often used as evidence for retrieval-extinction reflecting a wholly distinct process to standard extinction training remain inconclusive, as there is substantial overlap in the proposed neural substrates of reconsolidation and extinction. Hence, a combination of memory processes cannot be ruled out.

Other findings from animal models have been thought to pose a more serious challenge to the idea that retrieval-extinction procedures result in reconsolidation-dependent unlearning or updating. First, some animal studies have found that a retrieval trial *after* extinction can similarly attenuate spontaneous recovery and reinstatement (Baker, McNally, & Richardson, 2013; Beckers & Kindt, 2017; Millan et al., 2013; Ponnusamy et al., 2016). Extinction training performed before memory retrieval does not take place while the memory is in a purportedly malleable state, and so should not confer similar benefits to retrieval-extinction. Second, retrieval-extinction does not always protect against reinstatement and can even increase the return of both aversive and appetitive memories under certain conditions (Chan, Leung, Westbrook, & McNally, 2010; Millan et al., 2013). Even if only partial unlearning takes place during retrieval-extinction, this still ought to preclude the possibility of enhanced memory recovery.

In light of these findings, Hutton-Bedbrook and McNally (2013) suggest that, rather than updating the original memory trace, both retrieval-extinction and extinction-retrieval procedures might serve to facilitate discrimination between training and extinction conditions. The lack of reinforcement in multiple sessions or contexts highlights that a new, CS–no US contingency is in operation, and this could facilitate the selection of this CS–no US contingency memory at test, when the CS is also unreinforced.

Crucial to this concept of facilitated discrimination between learning and extinction is the prediction that, if signals are given that the old CS-US contingency is once again in operation, then retrieval-extinction or extinction-retrieval procedures should also facilitate a switch back to behavior that is in line with the originally learned contingencies. The order of the two is only crucial if it is assumed that extinction training must take place within the reconsolidation-window, and not if the brief reactivation and extinction sessions merely serve a contingency signaling function. Indeed, when retrieval-extinction trained rats in Millan et al. (2013) underwent testing in which nose-poking for alcohol was again contingently reinforced, they displayed higher levels of reacquisition than standard extinction-trained rats. In addition, although retrieval-extinction rats displayed less nose-poking at test if nose-poking was not reinforced, the time it took them to perform their first nose-poke was no different from extinction trained rats, suggesting that they were testing what contingency was in operation.

However, as previously mentioned, retrieval-extinction trained animals in Monfils et al. (2009) showed *reduced* reacquisition of fear when reexposed to reinforced CS presentations. While this is inconsistent with memory erasure, it is also inconsistent with enhanced discrimination between learning and extinction contingencies. Hence, facilitated discrimination between the contingencies in operation has trouble fully accounting for existing findings. In addition, the fact that retrieval-extinction and extinction-retrieval are procedurally similar and might similarly protect against reinstatement does not necessarily mean they reflect the same process. Tentative evidence to suggest that these procedures

might operate through different mechanisms comes from Ponnusamy et al. (2016), who found that while retrieval-extinction, extinction-retrieval, and immediate extinction all attenuated spontaneous recovery in rats relative to standard extinction, only retrieval-extinction-trained rats showed evidence of an intact STM trace after the intervention. However, we are unaware of any evidence for a dissociation of immediate and delayed effects on memory expression in human studies of retrieval-extinction procedures.

As with studies of the pharmacological blockade of reconsolidation, alternative explanations for retrieval-extinction effects come predominantly from animal research, with a paucity of human studies designed to tease out competing hypotheses. Though animal research allows a closer look at low-level mechanistic processes in the brain, behavioral studies in humans can also help resolve competing accounts. For example, a further prediction that can be gleaned from the "facilitated discrimination" account of retrieval-extinction is that it should not matter if the additional retrieval session is extended long enough to prevent the hypothesized labilization of the memory trace. If retrieval-extinction capitalizes upon the destabilization of memory then *multiple* retrieval trials before extinction should prevent the beneficial effects of retrieval-extinction, because multiple unreinforced trials appear to generate a "limbo" state between reconsolidation and extinction, or simply produce extinction (Merlo et al., 2014; Sevenster et al., 2014b). Such a procedure would not, however, disrupt the contingency signaling function of separated, unreinforced sessions proposed by Hutton-Bedbrook and McNally (2013). Though there is considerable research on spaced versus massed extinction, we do not know of any studies that have explicitly tested this in humans (but note that Ponnusamy et al., 2016 used three, rather than one, unreinforced CS presentations in their reactivation sessions, and still found a retrieval-extinction effect in rodents).

**Summary of retrieval-extinction procedures.** Table 3 provides an overview of retrieval-extinction procedures for aversive and appetitive memory. Retrieval-extinction procedures in humans may provide a purely behavioral means of attenuating reinstatement of fear responses, with a meta-analysis suggesting a small-to-moderate effect size (Kredlow et al., 2016). Experimental studies in humans have found reconsolidation-like effects using a 3-day design, and also shown a time-dependent interference effect of postretrieval extinction that is specific to the reactivated memory trace (e.g., Agren, Engman, et al., 2012). Hence, there is considerable evidence from human research into retrieval-extinction that is consistent with reconsolidation. However, a number of studies have failed to show any advantage of retrieval-extinction relative to standard extinction procedures. Reasons for these failures to replicate are worth investigating, and meta-analytic techniques could help in determining whether, overall, retrieval-extinction procedures appear to be effective in reducing fear.

When assessing retrieval-extinction studies for aversive memories, we noticed that a number of studies only reported and analyzed difference scores when assessing the return of fear (i.e., whether there is a difference between the CS+ and the CS−). This can cause problems in the interpretation of outcomes. Without seeing conditioned responses plotted on a trial-by-trial basis, it can be difficult to tell whether a lack of differences between a CS+ and CS− is due to a true loss of conditioned responses to the CS+, or an increase in conditioned responses to the CS−. It has been found that high trait anxiety predicts the generalization of conditioned responding to the CS− during reinstatement, and that this generalization can lead to a lack of differential responses to conditioned stimuli (Soeter & Kindt, 2010, 2012a). While lack of differentiation between the CS+ and CS− due to loss of fear to the CS+ is clearly desirable, lack of differentiation due to generalization of fear to the CS− is clearly not. Data should therefore be presented and analyzed in a manner that allows readers to distinguish between these two possibilities. We would suggest that researchers present conditioning data on a trial-by-trial basis, and also compare the first trial of conditioned responding after reinstatement or other "return of fear" procedures with the final trial of the previous session. In this way, responses can be seen in relation to the most recent learning experience, as well as relative to the other conditioned stimulus, and it is possible to confirm what is driving the observed outcomes.

In addition, retrieval-extinction studies using fear conditioning have sometimes reported strikingly different numbers of excluded participants, and though exact exclusion criteria and numbers excluded can be expected to vary depending on what the research is intended to investigate, it is not always obvious to readers why differences of quite such magnitude would be observed (e.g., six out of 71 participants reported in Schiller et al., 2010, vs. 53 out of 72 in Schiller et al., 2013). Quite large numbers of exclusions can be anticipated in fear conditioning studies, as many totally healthy participants do not even display basic conditioning processes such as acquisition and extinction, let alone reconsolidation-like effects. However, such exclusions can afford researchers some extra "experimenter degrees of freedom" (Wicherts et al., 2016). To avoid concerns about possible bias, it is advisable that researchers very clearly report all of the participants initially tested in a study, why different exclusions occurred, as well as when in the data collection or analysis pipeline such decisions were made. Though unexpected but entirely justifiable reasons for exclusion may occur during data collection and analysis, preregistration of already known exclusion criteria may also prove useful.

Animal research and two studies in human samples indicate that appetitive memories might also be amenable to retrieval-extinction procedures. While clinically significant changes following retrieval-extinction procedures in anxiety- and trauma-related disorders have not yet been convincingly demonstrated, two studies have demonstrated a positive impact of retrieval-extinction procedures on responses to addiction-related cues (Xue et al., 2012; Germeroth et al., 2017), and reduced self-reported drug consumption in one study (Germeroth et al., 2017). However, results from animal studies do raise some concerns about retrieval-extinction in the treatment of addiction (Millan et al., 2013). For this reason, critical tests of alternative explanations should be pursued.

As more research is conducted, it is also possible that other purely behavioral approaches geared toward disrupting or adaptively updating maladaptive memories will prove useful. Rather than extinction training after reactivation, some research suggests that counterconditioning (pairing conditioned stimuli with cues of the opposite valence to that which they were previously associated with) or cognitively demanding tasks may also produce beneficial changes in the strength or valence of memories. Das, Lawn, and Kamboj (2015) found that a brief reactivation of alcohol-related memories and a prediction error (being told not to drink a beer that the

Table 3
*Reviewed Studies of Retrieval-Extinction Interventions in Aversive and Appetitive Memory*

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Agren, Engman, et al., 2012 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min or 6 hr after reactivation | Yes* | Yes | — | — | Retrieval + extinction 10 min afterwards produced less reinstatement than extinction 6 hr afterwards. Björkstrand et al. (2015) tested 20 of the initial 22 participants at an 18-month follow-up, and found that results were sustained. Did not include a control for reactivation alone, extinction alone, or no reactivation + no extinction, but extinction outside the reconsolidation window may be considered a control for nonspecific effects of both reactivation and extinction. |
| Agren, Furmark, et al., 2012 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min or 6 hr after reactivation | Yes* | Yes | — | — | Genotyping indicated that the advantage for retrieval-extinction vs. retrieval + delayed extinction was related to dopamine- and serotonin-related genes. Did not include controls for reactivation alone, extinction alone, or no reactivation + no extinction, but extinction outside the reconsolidation window may be seen as a control for nonspecific effects of both reactivation and extinction. |
| Asthana et al., 2016 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | Yes** | — | — | — | Genotyping indicated that a retrieval-extinction advantage in SCR measures of spontaneous recovery was only present in met-allele carriers of the BDNF val66met polymorphism. Did not include controls for reactivation only or for no reactivation + no extinction. |

(*table continues*)

Table 3 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Björkstrand et al., 2016 | Responses to phobia-related stimuli | Retrieval-extinction | Extinction 10 min or 6 hr after reactivation | Yes* | Yes | — | — | Retrieval + extinction 10 min later reduced amygdala reactivity and increased willingness to view pictures of spiders in arachnophobic individuals, versus extinction outside the reconsolidation window. Control groups were within subjects. Björkstrand et al. (2017) found that behavioral effects were sustained at 6-month follow-up, and there was a trend for greater continued decreases in amygdala responsivity in the 10 min versus 6-hour group. |
| Das, Lawn, & Kamboj, 2015 | Alcohol related attentional bias, valuation, and craving in hazardous drinkers | Counter-conditioning | Counterconditioning 10 min after reactivation | Yes/RTD* | — | — | — | Included reactivation with prediction error (effective condition), no prediction error, and no reactivation group, but did not include a reactivation only control. Attentional bias, craving, and valuation of previously seen and novel alcohol cues were reduced in the reactivation with prediction error + counterconditioning group, but there were no group differences in alcohol consumption. |
| Fricchione et al., 2016 | Modified Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | No | — | No effect | — | Retrieval-extinction did not show advantages over standard extinction in SCR responses for spontaneous recovery, renewal, or reacquisition. |
| Germeroth et al., 2017 | Cue reactivity in nicotine addiction | Retrieval-extinction | Extinction 10 min after reactivation | — | — | — | — | Retrieval-extinction group displayed reduced cue-induced craving and smoked fewer cigarettes, with these outcomes sustained or emerging at 1-month follow-up. There were no group differences in urine cotinine, physiological responsivity, lapse, or relapse. Included extinction only + retrieval-extinction groups, without no reactivation only group or no reactivation + no extinction group. It seems unlikely that reactivation alone or no reactivation and no extinction would reduce craving. |

(*table continues*)

Table 3 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Golkar, Bellander, Olsson, & Öhman, 2012 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | No | — | No effect | — | Included separate experiments with fear-relevant and fear-irrelevant stimuli. Retrieval-extinction showed no advantage over standard extinction in either case, for FPS or SCR. |
| Gray & Teall, 2016 | PTSD | Range of therapeutic techniques after reactivation | Brief reactivation before several "dissociative experiences" | — | — | — | — | Uncontrolled case series |
| James et al., 2015 | Trauma film paradigm | Visuospatial task | Tetris gameplay 10 min after reactivation | ~No | — | — | — | Reactivation + Tetris group had significantly fewer intrusions than control groups. Including sufficient controls for a 2 × 2 interaction test but reported only one-way ANOVA with pairwise comparisons. Reanalysis of this data suggests a main effect of playing Tetris with no significant Reactivation × Intervention interaction (Hardwicke, 2017). |
| Johnson & Casey, 2015 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | Yes** | — | — | — | In both adolescent and adult samples, retrieval-extinction resulted in less SCR spontaneous recovery versus standard extinction. Did not include a control for reactivation only, or for no reactivation + no extinction. |
| Klucken et al., 2016 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | No | — | No effect | — | Retrieval-extinction showed no advantages over standard extinction in either SCR or fMRI measures. 62 of the initial 70 participants were included a follow-up session at 6 months, again with no advantage for retrieval-extinction. |

(*table continues*)

Table 3 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Liu et al., 2014 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min or 24 hr after reactivation | Yes* | ~Yes | Yes | — | Unconditioned stimulus reactivation + extinction attenuated reinstatement and spontaneous recovery of SCR relative to extinction alone, specifically for the reactivated memory. Effects also held for 2-week-old memory. Twenty-four of the initial 37 participants in Experiment 3 returned 6 months later, and the advantage of retrieval-extinction over standard extinction was still apparent. Time dependency of the intervention was demonstrated with a delay of 24 hr, rather than on the same day outside of the reconsolidation window. Did not include conditions with just reactivation or with no reactivation + no extinction, though extinction on a separate day to reactivation can be considered a control for nonspecific effects of both reactivation and extinction. |
| Maples-Keller et al., 2017 | Fear of flying | Retrieval-extinction | Extinction 10 min after retrieval | ~No | — | — | — | Assessed impact of four sessions of virtual reality reactivation (vs. no reactivation) followed by virtual exposure training for fear of flying. Clinical measures indicated no differences between groups, but physiological measures indicated possible advantage for retrieval-extinction group. Study included a 3-month follow-up. No control for reactivation alone, or for no reactivation + no extinction, though it seems unlikely that just a brief reactivation or no further intervention at all would have a significant impact on long-standing fear. |
| Meir Drexler et al., 2014 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | No | — | — | — | Retrieval-extinction did not provide advantages over standard extinction in SCR or expectancy ratings. |

(*table continues*)

Table 3 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Oyarzún et al., 2012 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | Yes** | — | Yes | — | Retrieval-extinction reduced SCR reinstatement vs. standard extinction, with effects specific to the reactivated memory. Used a within subjects control for reactivation. Did not include controls for reactivation alone or no reactivation + no extinction. |
| Schiller et al., 2010 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min or 6 hr after reactivation | Yes* | Yes | Yes | — | The results suggest that retrieval + extinction shortly afterwards reduced spontaneous recovery and reinstatement in SCR, specifically for the reactivated memory. Retrieval-extinction advantage was still apparent in a follow-up of 19 of the original 65 participants assessed 1 year later. Extinction training outside of the reconsolidation window may be considered a control for nonspecific effects of both reactivation and extinction. |
| Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | Yes** | — | Yes | — | Retrieval-extinction reduced reinstatement of SCR specifically for the reactivated memory. Five participants displayed the opposite pattern, with greater recovery for the retrieval-extinction stimulus. Did not include control for reactivation alone, or for no reactivation + no extinction. |
| Shiban, Brütting, Pauli, & Mühlberger, 2015 | Arachnophobia | Retrieval-extinction | Extinction 10 min after retrieval | No | — | — | — | Used virtual reality reactivation and exposure, and found spontaneous recovery was low regardless of the extinction procedure used, with no differences between retrieval-extinction and standard extinction. Study included a 6-month follow-up. |
| Soeter & Kindt, 2011 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | No | — | No effect | — | Startle for the reactivated stimulus was resistant to spontaneous recovery but not to reinstatement, and showed rapid reacquisition. Retrieval-extinction did not prevent spontaneous recovery of SCR responses. |

(*table continues*)

Table 3 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Soeter & Kindt, 2013 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | No | — | — | — | Retrieval-extinction did not prevent spontaneous recovery, reinstatement, or rapid reacquisition in FPS or SCR. |
| Steinfurth et al., 2014 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | Yes** | — | — | — | Retrieval-extinction procedure performed 1 week after initial learning reduced reinstatement vs. standard extinction. Did not include controls for reactivation only or for no reactivation + no extinction. |
| Telch, York, Lancaster, & Monfils, 2017 | Fear of spiders or snakes | Retrieval-extinction | Extinction 30 min after reactivation, or reactivation 30 min after extinction | Yes* | ~Yes | — | — | Compared retrieval-extinction with extinction-retrieval. Trend towards advantage for retrieval-extinction at posttreatment and marginally reduced spontaneous recovery at 3-month follow-up. Spontaneous recovery was low in both groups. Time dependency was demonstrated with post-extinction retrieval, rather than with delayed extinction after reactivation. Did not include controls for reactivation alone, extinction alone, or neither, but extinction before versus after reactivation may be seen as controlling for nonspecific effects of each. |
| Thompson & Lipp, 2017 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | Yes** | — | — | — | Unconditioned stimulus reactivation + extinction reduced SCR spontaneous recovery and reinstatement for fear relevant and irrelevant stimuli vs. standard extinction. Did not include controls for reactivation only or for no reactivation + no extinction. |
| Warren et al., 2014 | Pavlovian conditioning | Retrieval-extinction | Extinction 10 min after reactivation | No | — | No | — | Used a 2 × 2 design, with/without online expectancy rating and with/without retrieval before extinction. Spontaneous recovery and extinction did not appear to depend on whether the target memory was reactivated or not. |

(*table continues*)

Table 3 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Xue et al., 2012 | Cue reactivity in heroin addiction | Retrieval-extinction | Extinction 10 min or 6 hr after reactivation | Yes* | Yes | — | — | Retrieval + extinction 10 min afterwards reduced cue-induced craving vs. extinction alone or extinction outside the reconsolidation window. Included follow-ups up to 180 days postintervention, with a sustained advantage for retrieval-extinction participants. Did not include a reactivation only group, or no reactivation + no extinction group, but extinction outside reconsolidation window may be seen as control for independent effects of reactivation and extinction. |

*Note.* 1 = Reactivation × Manipulation interaction; 2 = Time dependency; 3 = Memory specificity; 4 = Dissociation of immediate and delayed effects; — = not assessed; RTD = effects were dependent upon the type of reactivation; No effect = procedures were put in place to test a criterion, but the absence of any effect of the intervention negated their use (e.g., time dependency cannot be assessed if the intervention has no effect regardless of time); FPS = Fear potentiated startle; SCR = Skin conductance response.
~ Represents that a criterion may have been imperfectly demonstrated, or that the interpretation of this demonstration as being consistent with reconsolidation is uncertain (e.g., if observed memory impairments rapidly recover). Reasons are discussed in the summary column and in the main text. * Represents that we believe there is sufficient grounds to infer a Reactivation × Manipulation interaction in a study, but that a strict 2 × 2 ANOVA with a test for an interaction was not conducted. ** Several retrieval-extinction studies using fear conditioning have not included controls for both reactivation alone and for no reactivation + no extinction. When other means of controlling for nonspecific effects have not been conducted (e.g., performing extinction outside the reconsolidation window), studies comparing only retrieval-extinction versus extinction alone raise difficulties for the inference of an interaction. As fear conditioning is a well-established paradigm and previous research suggests that fear memories would not be substantially affected by reactivation alone, or in the absence of reactivation or extinction, we have suggested that such studies may be reflective of an interaction. Readers may wish to be more or less lenient in their assessment, so we have designated these fear conditioning studies that miss both a control for reactivation alone, and for no reactivation + no extinction, with two stars. Studies missing multiple controls in less well-established paradigms or in clinical translation attempts have been noted as "not assessed."

participant had been expecting to consume), followed by disgust-inducing counterconditioning (pairing of alcohol cues with disgusting images and extremely bitter liquids), had an impact on maladaptive memory expression in problem drinkers. Participants who underwent the prediction error reactivation + counterconditioning displayed lower valuation of alcohol cues and less attentional bias toward them compared with participants who received counterconditioning alone or reactivation without a prediction error + counterconditioning.

For aversive memories, James et al. (2015) found that reactivation of memories for a traumatic film followed by playing the computer game Tetris reduced later intrusive memories for the film material. Such a procedure may have utility in tackling the disturbing flashbacks people experience in the aftermath of trauma. However, it has been noted that although group by group comparisons in this study suggest an advantage for the Tetris + memory reactivation group relative to Tetris alone, reactivation alone, or no intervention, a significant Reactivation × Manipulation interaction was not actually present, with a memory reactivation (reactivation vs. no reactivation) by Tetris manipulation (playing vs. not playing Tetris) 2 × 2 ANOVA revealing only a significant main effect of Tetris (Hardwicke, 2017, pp. 107–108). Of course, in the framework of null hypothesis significance testing, absence of evidence for an interaction is not the same as evidence for the absence of an interaction; it may be that the study was underpowered to detect an interaction. Nevertheless, the study does not currently provide unambiguous evidence indicating an interaction between reactivation and playing Tetris. Further experimental research on these approaches, and other behavioral interventions inspired by the idea of reconsolidation, as well as tests of their efficacy in ameliorating clinical pathology, are certainly warranted.

Both these novel behavioral approaches aimed to demonstrate reconsolidation-like effects using conditions such as reactivation alone, intervention alone, and the combination of reactivation and intervention that are necessary for making basic claims of having demonstrated reconsolidation as a mechanism of action. Some other behavioral approaches claiming to tap into the phenomenon of reconsolidation have not been equally rigorous. For example, a patent-pending approach to the treatment of PTSD, adapted and renamed from the "visual-kinesthetic dissociation" protocol of neurolinguistic programming practitioner John Bandler (1985), has been dubbed the Reconsolidation of Traumatic Memories (RTM) approach (Gray & Teall, 2016). This therapeutic approach may be effective, and may even operate through reconsolidation, but the primary reason it seems to have been named after reconsolidation is because the procedure begins with a reactivation of the target memory before performing further therapeutic techniques. The fact that the outcomes are apparently inconsistent with extinction (e.g., because effects are observed more quickly than in typical exposure-based approaches, and are said to be more long-lasting) does not make reconsolidation the default explanation. We are not aware of any controlled studies that have aimed to verify whether the unique ordering or specific combinations of techniques that are argued to allow this approach to leverage the power of reconsolidation are necessary to produce the observed effects. If reactivating a memory and engaging in further therapeutic work is to be the only requirement for an intervention to be deemed a reconsolidation treatment, then almost any psychological therapy, be it cognitive therapy, psychoanalysis, or even basic counseling, is likely to meet it in many circumstances. Although it has been argued that reconsolidation may play a role across a whole range of psychotherapies (Lane, Ryan, Nadel, & Greenberg, 2015), extending the concept of reconsolidation so broadly may render it effectively meaningless.

## Declarative Memory Reconsolidation

**Experimental studies.** Psychological research has long demonstrated the malleability of human declarative memory (Bartlett, 1920; Loftus & Palmer, 1974). When remembering information, people are known to distort, misattribute, and even confabulate the content and sources of their memories (Schacter, 1999). Reconsolidation has been suggested as a possible mechanism to explain some of these findings, potentially bridging the divide between cognitive science and neurobiology (Hardt, Einarsson, & Nader, 2010). Several labs have conducted research to assess whether they can induce changes in human declarative memory that are consistent with reconsolidation. We first discuss two paradigms for which multiple studies have been conducted (object list learning and paired associate learning), before considering several studies from a wider range of labs and experimental tasks.

***Object list learning.*** Hupbach, Gomez, Hardt, and Nadel (2007) used an object learning paradigm, in which participants were shown and asked to memorize a set of 20 objects (Set 1) in a particular context on Day 1. On Day 2, two groups of participants learned a second set of objects (Set 2), which were presented to participants in a different fashion, so as to reduce incidental reactivation of the Set 1 memory. Participants in the reminder group learned Set 2 in the same room as Set 1, and—as a brief reminder—were asked by the experimenter (the same person as on Day 1) to describe the procedure of the first session. Participants in the no-reminder group underwent Set 2 learning in a different room and were not prompted by the experimenter (a different person than on Day 1) to recall the previous procedures. A third group served as a control group and omitted Day 2 learning altogether. At testing on a separate day, participants were required to recall the objects from Set 1.

Hupbach et al. (2007) found that participants in the reminder group intermixed significantly more items from Set 2 into Set 1 recall than those in the no-reminder or control groups. This intrusion effect did not appear to result from simple source confusion, because participants in the reminder group did not mistakenly intermix items from Set 1 into recall of Set 2 (Hupbach et al., 2007, Experiment 3). Moreover, when participants were presented with the objects they had seen in a recognition test, they also misattributed Set 2 items to Set 1, but not vice versa (Hupbach, Gomez, & Nadel, 2009). This asymmetry in intrusions was argued to reflect a reactivation-dependent destabilization of the memory, enabling items from Set 2 to be incorporated into the Set 1 memory. That this might be an example of reconsolidation was further supported by the finding that such intrusions did not occur if Set 1 was recalled shortly after Set 2 learning (Hupbach et al., 2007, Experiment 2), suggestive of the retention of a STM trace. This study demonstrated that reactivation + new learning produced different effects to new learning in the absence of reactivation, but did not also include a reactivation only control for a clear demonstration of a Reactivation × Manipulation interaction. However, given that

the key outcome variable was the intermixing of items from the newly learned list into the previously learned list, it would not be expected that reactivating List 1 without subsequent List 2 learning would somehow lead to intrusions of the unknown List 2 items into List 1. Hence, the key criterion for these studies would be that intrusion effects are reactivation-dependent, rather than demonstrating a Reactivation × Manipulation interaction, and this was found. The study additionally demonstrated a dissociation of immediate and delayed effects. The basic finding of increased intrusions from Set 2 into Set 1 as a consequence of reactivation has since been replicated in a sample of young adults by an independent research group (though elderly adults displayed greater intrusions when memory was *not* reactivated; Jones, Pest, Vargas, Glisky, & Fellous, 2015).

These findings were developed in subsequent studies using the same paradigm. First, Hupbach, Hardt, Gomez, and Nadel (2008) showed that returning participants to the initial context in which they had learned Set 1 before learning Set 2 was necessary and sufficient for triggering these reconsolidation-like effects. However, when a context was overly familiar, which is argued to prevent the reactivation of a specific memory via that context, alternative means of reactivation—such as a reminder question or using the same experimenter—effectively rendered the memory vulnerable to intrusions (Hupbach, Gomez, & Nadel, 2011). This study was also notable in replicating the findings of Hupbach et al. (2007) in a sample of 5-year-olds. In addition, Hupbach (2015) found that reactivation *per se*, followed by new learning, was not sufficient to induce an asymmetry in intrusions: While a contextual reminder produced these effects, if reactivation was extended to include a test on the Set 1 items before learning of Set 2, then intrusions from Set 2 into Set 1 did not differ from the no reminder group. Hence, as has been discussed above in relation to memory destabilization in studies of human and animal fear conditioning, and is shown next with regards to another human declarative memory paradigm (Forcato et al., 2007), there is evidence for boundary conditions on the induction of reconsolidation-like effects in human declarative memory.

Interestingly, unlike an abundance of animal reconsolidation studies and many human studies above, in which target memories were impaired due to reconsolidation-based interventions, the general observation in these object list learning studies is that the original Set 1 memory is not necessarily impaired, but rather modified with the inclusion of items from Set 2. This finding also differs from initial observations demonstrating the malleability of human memory, in which memories appeared to become highly distorted, not merely added to (Bartlett, 1920; Loftus & Palmer, 1974). Using a variation of the Hupbach paradigm with IAPS images, Wichert, Wolf, and Schwabe (2013a) did observe reductions in recognition accuracy when reactivation was combined with new information, provided that there were several presentations of the new information. Other studies using pictures and post-retrieval learning, however, have found that new learning can have an effect regardless of whether it is preceded by reactivation, and irrespective of how many times the new information is presented (van Schie, van Veen, Hendriks, van den Hout, & Engelhard, 2017b; van Schie, van Veen, van den Hout, & Engelhard, 2017a). Indeed, Hupbach (2015) found a main effect of new learning on impairment of List 1 recall regardless of reactivation (i.e., intrusions into list 1 were reactivation dependent, whereas poorer recall of List 1 was dependent upon new learning even if reactivation did not occur).

Though findings from the lab of Hupbach and colleagues (e.g., Hupbach et al., 2007, 2008) have been consistent, Klingmüller, Caplan, and Sommer (2017) were unable to replicate the basic finding of asymmetric intrusions. After an initial failure to replicate Hupbach and colleagues' findings (Experiment 1), Klingmüller et al. (2017) changed their experimental setup so that the two rooms in which objects were learned were highly unusual and markedly different from one another (Experiment 2). They did then observe some intrusions of List 2 objects into List 1, though the magnitude of this effect was not as great as in Hupbach et al. (2007, 2008). Klingmüller et al. (2017) favored a "contextual binding" account of these intrusions over a reconsolidation account (see the Alternative Explanations section below).

***Paired associate learning.*** Using a different paradigm, Forcato et al. (2007) have also generated results consistent with reconsolidation in human declarative memory. In Forcato et al.'s (2007) study (and in Forcato, Argibay, Pedreira, & Maldonado, 2009), a contextual reminder combined with an intervening list of nonsense syllables did not result in directly observable alterations to the original memory. However, memory disruption was inferred due to the absence of retrieval induced forgetting (RIF) caused by List 1 memory (cf. Anderson, Bjork, & Bjork, 1994). RIF denotes the impaired recall of an item because a related item has been recalled. This phenomenon has been argued to reflect the inhibition of items that might compete with the target item for retrieval (Anderson et al., 1994; though see Alternative Explanations below for a different account of RIF). In the context of these studies, if memories for List 1 are retained, then attempts to recall them at testing should produce RIF for the related but competing memories for List 2. Hence, memory disruption for List 1 would be shown by unimpaired recall of List 2 when it occurs after testing for List 1 (the absence of RIF). Where List 2 recall is impaired after List 1 recall, it is possible to show that List 2 memories are not actually disrupted, because if List 2 is tested before List 1, recall is unimpaired.

Forcato et al. (2007) first demonstrated that memory consolidation of a list of nonsense syllable pairs could be disrupted if participants were required to learn a second list 5 min but not 24 hr afterward. List 1 memory appeared resistant to the interfering effects of List 2 learning if this was conducted 24 hr later. However, if a brief reminder of List 1 was given 5 min before learning List 2, then new learning produced similar interference effects as when List 2 training occurred shortly after initial List 1 learning. Similarly to the studies of Hupbach and colleagues, as the crucial outcome measure in these experiments was reliant upon the presence of initially and subsequently learned information, the demonstration of a Reactivation × Manipulation interaction was not possible, as RIF requires testing the recall of the interfering information that is used as the postreactivation manipulation. Results did, however, appear to be reactivation-dependent, as new learning in the absence of prior memory reactivation did not prevent RIF induced by List 1 recall. In addition, interfering effects of postreactivation learning were apparent when List 2 learning occurred 5 min or 6 hr, but not 10 hr, after List 1 reactivation. This demonstration of time dependency of the intervention, albeit indicative of a longer period of memory instability than might be expected based on other studies of reconsolidation, might be taken

as further evidence that nonspecific effects of memory retrieval or of new learning do not explain the results.

It was also found that certain types of reactivation, and the presumed subsequent reconsolidation, might enable alterations in the strength of human declarative memories. Giving participants two or four cue-reminders significantly enhanced their memories at testing relative to one cue reminder, or to multiple cue-response reminders that allow the participant to respond to the cue reminder (which do not appear to labilize the memory trace: Forcato, Rodríguez, & Pedreira, 2011). Consistent with a reconsolidation account, these enhancing effects were not evident when memories were tested shortly after the experimental manipulation. Providing one or two cue-reminders a day after learning also resulted in greater persistence of memory at a test 6 days later, though enhancing effects of reactivation were not observed if reminders were given a week after the initial learning (Forcato, Fernandez, & Pedreira, 2013). Manipulations such as a mild stressor or the administration of clonazepam after a cue-reminder have also been found to improve recall in this paradigm, again with no influence at short-term testing (Coccoz, Maldonado, & Delorenzi, 2011; Rodríguez et al., 2013).

Not all declarative memory research supports these results. Potts and Shanks (2012) found that testing memories for word pairs (English words paired with novel Swahili words) learned the day before actually *protected* the initially learned associations against interference from new associations learned on Day 2, consistent with previous literature indicating that retrieval practice can improve memory (Karpicke & Roediger, 2008). Similarly, Hardwicke et al. (2016) found that a reactivation phase prior to learning new number or letter sequences resulted in less impact of new learning in comparison to new learning alone. However, retrieval is not synonymous with the induction of reconsolidation. Potts and Shanks (2012) tested their participants on the full list of initially learned word associations before presenting new word pairs, and Hardwicke et al. (2016) had participants recall and then restudy sequences from the previous day. Such extended reactivation may not be optimal for triggering memory reconsolidation, and is more akin to practice or rehearsal than to a brief reminder typically thought to trigger reconsolidation.

Similarly to Hupbach (2015); Forcato et al. (2009) found that parameters of the reactivation session determined whether interference effects occurred. Disruptive effects of new learning were only observed if the cue-reminder was presented without the possibility of completing a response. Although it is clear that certain characteristics of memory reactivation can determine whether reconsolidation-like effects are observed, it should be highlighted that this is not always consistent across studies from different groups. Several declarative memory studies discussed below (e.g., Chan & LaPaglia, 2013) also allowed participants to respond to cued memory questions during recall, and observed effects that they attribute to reconsolidation.

***Modulation of declarative memory reconsolidation by emotion and stress.*** A wealth of research shows that important, emotional, or arousing events can produce particularly strong (though not necessarily accurate: Neisser & Harsch, 1992; Talarico & Rubin, 2003) declarative memories (Brown & Kulik, 1977). Studies into the consolidation of memory suggest that adrenal hormones released in response to stress can serve to enhance memory (McGaugh, 1989; McGaugh & Roozendaal, 2002; Roozendaal, 2002), though intense stress or very high doses of stress hormones may also result in memory impairment (Baldi & Bucherelli, 2005; McGaugh, 1989; Salehi, Cordero, & Sandi, 2010). Researchers have investigated whether stress manipulations might also modulate memory strength when administered within the putative window of reconsolidation.

Using the paired associate paradigm, Coccoz, Maldonado, and Delorenzi (2011) found that administering a mildly stressful cold pressor test (CPT) following a cue-reminder 6 days after initial learning enhanced participants' recall a day later, but not 3 hr after, relative to control participants. These findings have found mixed support from other studies of the effects of stress on declarative memory. In two experiments, Bos, Schuijer, Lodestijn, Beckers, and Kindt (2014) found that a socially evaluated cold pressor test (SECPT) following reactivation enhanced declarative memories for lists of neutral, positive, and negative words. Likewise, Marin, Pilgrim, and Lupien (2010) found that having participants undergo a Trier Social Stress Test (TSST, a social stress induction where participants are required to prepare and deliver a speech under time pressure; Kirschbaum, Pirke, & Hellhammer, 1993) after recalling neutral and emotional story slides enhanced memory for emotional slides at an immediate test, as well as 5 days later. These three studies all found evidence indicative of a Reactivation × Manipulation interaction. Whereas Coccoz et al. (2011) found a dissociation of immediate and delayed effects, this was not the case in Marin et al. (2010), as the effect of the manipulation was observed immediately. An immediate test following the stress manipulation was not conducted in Bos et al. (2014).

In contrast to stress-induced enhancement of memory, other studies have found that stress can actually impair memory after reactivation, or at least prevent its facilitation. For example, Schwabe and Wolf (2010) found that a postreactivation SECPT impaired later recall of neutral episodic memories, with no effect on positive or negative memories. In another study by Hupbach and Dorskind (2014), participants were trained to associate images of animals with unrelated images of objects. Two days later, participants were presented with half of the animal images again, and then subjected to a cold pressor stress test or warm water control condition. At a memory test another 2 days later, participants in the warm water condition were found to have enhanced memory for the objects associated with reactivated animal images, relative to nonreactivated images. In contrast, participants who underwent the stress induction following reactivation displayed no such enhancement effect. Hupbach and Dorskind (2014) concluded that stress can impair the reconsolidation of declarative memory. Both Schwabe and Wolf (2010) and Hupbach and Dorskind (2014) found outcomes consistent with a Reactivation × Manipulation interaction, with Hupbach and Dorskind's (2014) study of further note for showing that the manipulation was specific to the reactivated memories. Other research has found no effect of an arguably stressful aversive procedure (Pavlovian fear conditioning) on the later expression of declarative memory (Fernández, Bavassi, Kaczer, Forcato, & Pedreira, 2016, Experiment 3).

Given that very similar stress manipulations were used across these conflicting studies—showing both improvement and impairment of memory after postreactivation stress—it seems unlikely that the magnitude of the stress experienced by participants could explain the inconsistent findings (with the exception of the use of

Pavlovian conditioning in Fernández et al., 2016). Although all these studies were of declarative memory, the actual tasks diverged significantly. Future research could aim to elucidate how robust these findings are (i.e., in direct replications), and whether differences in the type of memory tasks used are associated with different outcomes as a result of post-reactivation stress. Furthermore, it may be informative to assess how specific aspects of the stress response (e.g., particular physiological responses) are related to subsequent alterations in memory, and how these effects may be modulated by situational factors (e.g., timing, context) and individual differences (e.g., trait anxiety, learning history). Such situational and individual difference variables have been found to affect the impact of cortisol (a major component of the stress response) on memory formation and expression, and might be expected to modulate reconsolidation as well (van Ast et al., 2013).

Researchers have also investigated whether stress might affect the "updating" of declarative memories with new information after reactivation, using the TSST as a stress manipulation. For the object list learning paradigm, Dongaonkar, Hupbach, Gomez, and Nadel (2013) found that stress after (Experiment 2), but not before (Experiment 1), memory reactivation and new learning reduced later intrusions from the newly learned material, while leaving recall for the list 1 items unaffected. Schmidt, Rosga, Schatto, Breidenstein, and Schwabe (2013) found that a stress induction before the reactivation of memories for film clips protected those memories from the incorporation of misleading information that was given in postreactivation questionnaires (Schmidt, Rosga, Schatto, Breidenstein, & Schwabe, 2013). Neither of these studies included conditions assessing what the outcome of stress induction on later memory would be without memory reactivation (Experiment 1 of Dongaonkar et al., 2013 did, but this experiment showed no significant effect of stress). Both studies indicate that stress may reduce intrusions of new information into old memories, but found this protective effect to occur when stress was provoked at different time points, and did not establish that these results were dependent upon reactivation before new learning.

Instead of a stressor, Strange, Kroes, Fan, and Dolan (2010) used fearful (vs. neutral) faces as aversive emotional stimuli. Faces were presented at various time points among word stems used to trigger recall of items learned on the previous day. They found that fearful but not neutral faces produced amnesia for the preceding noun, and that this amnesia was only revealed at delayed testing. The results are therefore consistent with a within subjects Reactivation × Manipulation interaction, further suggesting a dissociation of immediate and delayed effects. Impairments in memory only occurred for words that were successfully recalled upon cueing with the word stem, thus suggesting that the effects are specific to the reactivated memory (although all words underwent partial reactivation via word-stem presentation). The results pose some difficulties for a reconsolidation interpretation, in that the effect of the manipulation was time-dependent, but on a scale of seconds: Only the very preceding word was affected by the presentation of a fearful face. The unstable state of memory after the induction of reconsolidation is typically thought to last for some hours, rather than seconds, after reactivation. Hence, it may be argued that the corruption of memories by emotional stimuli ought to affect other reactivated memories than just those immediately preceding the amnestic stimulus. On the other hand, certain types of intervention may have to take place within very restricted time frames in order to have an effect, even if the memory is not restabilized over such a short time.

Memory modulation caused by emotional events is thought to be partly dependent on amygdala activation and noradrenergic activation during learning, or after retrieval, which can be blocked by the betablocker propranolol (Cahill et al., 1994; Roozendaal, 2002). As discussed above, reconsolidation for emotionally arousing events can be disrupted by propranolol (Debiec & LeDoux, 2004; Kindt, 2014, see Pharmacological Disruption of Aversive and Appetitive Memory Reconsolidation section above), suggesting that emotionally valenced episodic memories might also be vulnerable to interference. Tentative evidence for such an effect has indeed been observed (Kroes, Strange, & Dolan, 2010). In this study, participants who received propranolol 90 min before memory reactivation did not display the memory enhancement for emotional words that was apparent in the placebo group. This lack of enhancement was already apparent during retrieval under the influence of propranolol, and persisted at testing on a subsequent day. Items that were not reactivated displayed normal emotional enhancement at delayed testing in the propranolol group, thereby suggesting a Reactivation × Manipulation interaction (using a within subjects control for reactivation) and memory specificity, but providing evidence against a dissociation of immediate and delayed effects. A reconsolidation interpretation is complicated by the fact that words that were not successfully recalled at retrieval were the ones that remained irretrievable at test. Emotional words that were successfully recalled under the influence of propranolol were typically still remembered. This conflicts with other studies, in which accurate retrieval of words was necessary for the induction of reconsolidation-like effects (Strange et al., 2010). While some research indicates that full retrieval might not trigger memory labilization, preventing participants from giving a response after reactivation—as in Forcato et al. (2009)—is not the same as participants failing to retrieve an item when given the opportunity, as in Kroes et al., (2010). The idea that reactivation was necessary to produce these effects is therefore complicated, as words for which there was clear evidence of reactivation were apparently not affected.

Other studies administering propranolol prior to reactivation have also found that propranolol + reactivation can abolish emotional enhancement effects, as well as the feeling of remembering associated with negative emotional pictures (Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012; Schwabe, Nader, & Pruessner, 2013). Both these studies included control groups and statistical analyses to demonstrate a clear Reactivation × Manipulation interaction, but did not assess performance in a short-term test. One further study failed to find any effect of prereactivation propranolol on either immediate or delayed testing, but did observe a reduction in declarative memory performance for both neutral and emotional items when cortisol was used (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009). This study did not include a no reactivation condition, so it cannot be assumed that such effects of cortisol were reactivation dependent.

In all of these studies, propranolol was administered before the memory reactivation phase. Therefore, it is possible that, instead of blocking reconsolidation, propranolol exerted an influence on retrieval or new learning/encoding that produced a lasting effect on the memory. An ideal test of a reconsolidation mechanism would involve administering propranolol after reactivation to reduce the

likelihood of alternative explanations, such as disruption of retrieval or new encoding. Schwabe et al. (2012) found no effect of propranolol on brain activity during memory reactivation, which would indicate a lack of impact on retrieval processes, but Kroes et al. (2010) observed a clear modulatory effect of propranolol at retrieval. Further research found that, at least in a paradigm using an emotional story presented in the form of a slideshow, only propranolol administered before reactivation produced later deficits in declarative memory, with no effect of postreactivation propranolol (Thomas, Saumier, Pitman, Tremblay, & Brunet, 2017). This could suggest that there is some effect of propranolol on the encoding or retrieval of emotional declarative memory that is long lasting, rather than an effect on reconsolidation. However, it could also be that the reconsolidation window for reactivated memories in these paradigms is significantly shorter than that observed in fear conditioning studies using propranolol, such that postreactivation propranolol reaches its peak bioavailability too late to interfere with reconsolidation.

***Brain stimulation and declarative memory.*** As well as aiming to disrupt or change memories with pharmacological agents or interfering learning, various means of stimulating the brain, either electrically or with magnetic fields that produce electrical currents in the brain, are available. Two of the earliest studies investigating retrieval-induced memory vulnerability in humans involved electroconvulsive shock (Rubin, 1976; Squire et al., 1976), which was thought to disrupt reactivated memory engrams (Misanin et al., 1968). While Rubin (1976) found some success in delivering ECS in time with patients' symptom reactivation, Squire et al. (1976) results were less promising. Squire et al. (1976) gave depressed participants a battery of memory tests and also had them recall some verifiable remote memories. Material learned 10 min prior to ECT, which was performed under anesthetic, was subsequently less well remembered. However, participants who learned information 14 hr–18 hr earlier and were then given a test of their memories 10 min before ECT did not have significantly worse memories for the material than those who did not receive a test. Remote memories were likewise unaffected. However, it should be noted that participants' memories were tested 6 hr–10 hr after ECT, potentially precluding the observation of delayed effects of the intervention.

Kroes et al. (2014) more recently used ECT in depressed patients. One week before ECT, patients learnt two stories presented in a slideshow format. Approximately 4 min before ECT, one of the stories was reactivated by presenting the participants with a slide from the story. Participants were asked to remember what was behind certain places where the slide had been masked, and were then anesthetized before receiving ECT. One group of participants received a STM test 29 min–133 min after ECT, whereas the other group was tested the following day. A third group did not receive ECT and was also tested 1 day after memory reactivation. Whereas participants who were tested shortly after ECT had equivalent memory scores for the reactivated and nonreactivated stories, those who were tested the day after had significantly poorer memory for the reactivated than the nonreactivated story. In contrast, participants who did not receive ECT had enhanced memory for the reactivated story. These findings are consistent with a Reactivation $\times$ Manipulation interaction, the effects of which are disclosed at delayed but not immediate testing, and which are specific to the reactivated memory.

Some methodological factors present some challenges for interpretation. In the no-ECT group, memories were reactivated in the same room as that in which testing occurred, whereas they were reactivated in the ECT room for the other two groups. Enhanced memory specifically in the no-ECT group might thus reflect contextual cueing of the memory. In addition, the lack of a STM test in a separate no-ECT group complicates interpretations of how ECT affected memory in the short-term, as there is no comparison group: It could be that ECT had a disruptive effect even at short-term testing, just to a lesser degree than when the memory was tested after a delay. However, including so many groups in an ECT patient study such as this is highly demanding, and the difference between the reactivated and nonreactivated memories disclosed in the ECT + reactivation group at long-term testing is in line with disruption of the reactivated memory despite these limitations. Moreover, supplementary analyses indicated that the type of ECT performed determined whether effects of the intervention were observed, which also suggests that the intervention itself, rather than confounding effects such as contextual cueing, likely explain the results.

Less intense means of stimulating the brain are also available to researchers. Sandrini, Censor, Mishoe, and Cohen (2013) assessed the effect of 1Hz rTMS delivered to the right dorsolateral prefrontal cortex (DLPFC) after reactivation on subsequent declarative memory. Similarly to the object list learning studies above, on Day 1, participants learned a list of objects (words for objects were written on cards, rather than objects themselves) in a particular room. On Day 2, participants' memories were reactivated by returning them to the same room with the same experimenter, and asking them to recall the procedure from the previous day. Ten minutes after this reactivation, one group received rTMS of the right DLPFC, and another received stimulation of the vertex (a control stimulation region). A third group received rTMS of the right DLPFC without reactivation. On Day 3 participants were required to recall as many words from the list as possible. In a second experiment, participants underwent reactivation and DLPFC or vertex stimulation, and were tested on the same day. When tested on Day 3, participants who received reactivation and stimulation of the right DLPFC exhibited significantly greater memory performance than the control stimulation and no reactivation groups. In contrast, at short-term testing 30 min after the stimulation, there were no differences between the reactivation + DLPFC stimulation group relative to the reactivation + vertex stimulation group.

These findings would suggest that DLPFC activation given after reactivation can result in enhancement of declarative memory, revealed only at later testing, thus suggesting both a Reactivation $\times$ Intervention interaction (though without a control for no reactivation + no stimulation), as well as a dissociation of immediate and delayed effects. However, comparing the percentage of items recalled in the short-term test relative to the long-term test does not support the idea of a delayed enhancement of memory brought about by DLPFC stimulation that is only revealed at later testing. The performance of the reactivation + DLPFC stimulation group appears to have already been at a level comparable to that exhibited at longer-term testing when tested shortly after stimulation, but the control stimulation group was also performing at a higher level than when assessed at a delayed test. It might be that rather than "enhancing" memory after reactivation via reconsoli-

dation, the stimulation reduced the decay of memory that otherwise occurred in control conditions by the time of long-term testing. Hence, these results should be interpreted with some caution. Further complicating interpretation of the role of the DLPFC and how its stimulation might affect reconsolidation, DLPFC excitation induced by anodal transcranial DC stimulation (tDCS) was found to improve declarative memory in one study, regardless of whether or not memory was reactivated (Sandrini et al., 2014).

***Naturalistic declarative memory paradigms.*** Most research on declarative memory reconsolidation has been conducted using relatively artificial paradigms that may bear little relation to things we typically need to remember in daily life. Importantly for the relevance of such research to our understanding of how memory works under real-world conditions, effects of postreactivation interference have been observed for naturally occurring memories formed outside of the lab, as well as in lab tasks. Schwabe and Wolf (2009) found that participants' memories for a recent neutral (but not emotional) autobiographical event were impaired if they learned a new story after memory reactivation, demonstrating a clear Reactivation × Manipulation interaction for naturalistic memories. As noted above, Schwabe and Wolf (2010) also found that a mild stressor given shortly after memory reactivation impaired neutral memories formed outside of the lab.

Using an alternative episodic memory paradigm, Chan and LaPaglia (2013) demonstrated that memories for an engaging TV drama could be impaired following reactivation combined with misinformation. Participants watched an episode of the TV series *24*, which features a fictional terrorist attack. They then had their memories reactivated (vs. not reactivated) before receiving misinformation that was designed to supplant the original memory. Whether or not the misinformation was given was manipulated within subjects, such that only certain parts of the story were targeted with misinformation. Chan and LaPaglia (2013) found that participants were significantly worse at recognizing correct information when they had been misinformed, and that this effect was only present when misleading information followed reactivation, suggesting a Reactivation × Manipulation interaction.

However, only one of the experiments conducted by Chan and LaPaglia (2013) used an appropriate 3-day design to allow time for the memory to consolidate, and for the reactivated memory to reconsolidate (Experiment 6). The experimental effects were not entirely consistent with reconsolidation, as they were already present at short-term testing (Experiment 3). Evidence for time dependency of the manipulation presented in the study is also suboptimal. Experiment 2 demonstrated that misleading information given 48 hr after reactivation—thus outside the reconsolidation window—did not lead to poorer memory performance. Given that a number of other mnemonic processes could have occurred over the intervening days and nights of sleep, it would have been preferable to conduct the test of time-dependency outside the expected reconsolidation window but on the same day as reactivation. In addition, this experiment was not conducted using a delayed memory test, and thus only assessed an immediate impact of misleading information on memory.

Chan and LaPaglia's (2013) results are consistent with memory specificity (Experiment 5), as only misleading material that was related to the original memory had an interfering effect. Hence, one would not expect that the manipulation was producing a general amnesic effect. However, this experiment only assessed memory shortly after the intervention, without a 24-hr delay between interference and testing. Further complicating the interpretation of these results, other research suggests that the true/false and "source free" memory tests used by Chan and LaPaglia (2013) do not rule out alternative explanations, such as that the original memory was still present but no longer deemed accurate by the participants (Rindal, DeFranco, Rich, & Zaragoza, 2016; see Alternative Explanations section below). Hence, there are some serious limitations to the conclusions we can draw from this study regarding reconsolidation.

In one further example of a naturalistic paradigm, St. Jacques and Schacter (2013) had participants go on a museum tour while wearing a small camera that continuously photographed what they saw. On a subsequent day, participants were presented with pictures that had been taken by their camera, depicting specific points in the tour. After this reactivation, participants were presented with false images taken from museum stops that the participants had not been to, and were asked whether these had been seen on the previous day. On a final day of testing, participants were exposed to images of museum stops they had been to as well as a number of false images depicting stops they had not attended. It was found that memory reactivation before the presentation of false images led to both greater recognition of correct images and higher false alarm rates for false images. In a further analysis, St. Jacques and Schacter (2013) found that the strength of reactivation, as indexed by the amount of subjective reliving during recall, was positively correlated with both increases in later recognition and higher endorsement of false images. St. Jacques and Schacter (2013) included a within subjects control for reactivation but do not appear to have included a control for the manipulation (the presentation of images from museum stops that had not been attended), meaning that a clear Reactivation × Manipulation interaction was not established (it should be noted that this experiment was in fact not specifically designed with the intention of demonstrating reconsolidation). In addition, measures of hits and false alarms for the nonreactivated photos were subtracted from the different reactivation conditions, making interpretation of whether results in the reactivation conditions are significantly different from nonreactivated memories difficult to determine.

**Practical and clinical applications of declarative memory reconsolidation.** More tests of how findings from experimental research on reconsolidation relate to naturalistic memories are certainly warranted. The results of the above studies suggest that reactivation-dependent changes in later recall and recognition are not restricted to simple lab tasks, but do not go especially far in telling us how reconsolidation-like effects might be of relevance in our daily lives, in clinical settings where memories are discussed, or in legal settings where the veracity of memory may be of paramount importance.

If misleading information can really change reactivated memories, perhaps even rendering the original memory trace irretrievable or fundamentally corrupted, then this could have considerable implications in legal proceedings. For example, it would be very important when collecting witness statements not to present information or suggestions beyond what the witness recalls, as this might be incorporated into the reactivated memory and later recalled as if actually experienced. Though misleading information should be avoided regardless of whether reconsolidation underpins

some already well-studied false memory effects, discovering that memories are directly changed under certain conditions could highlight the importance of not contaminating eyewitness evidence, just as strict procedures should be followed for physical evidence. In clinical settings, it would be important to know whether the different interpretations and framing of memories and experiences offered by the therapist, or generated by the patient, result in actual distortions of the original memory at later dates, or whether they are recognized as being alternative perspectives on an event that remains well-remembered. Disruption of declarative memory as a result of pharmacological treatments aiming to diminish maladaptive emotional memories might also raise concerns for eyewitness testimony following traumatic experiences (Elsey & Kindt, 2016).

Before strong conclusions can be drawn as to the relevance of declarative memory studies in these wider domains, it would be interesting to know the extent to which distortions of memory are resistant to later corrective information (e.g., whether participants easily accept that false alarms were not really seen, and ultimately recognize correct items when told these are correct), and how robust such changes are over time. Further studies of purely naturalistic memories from participants' daily lives over a range of time periods could also be conducted.

**Alternative explanations.** Using an established computational model of declarative memory—the temporal context model (TCM)— Sederberg et al. (2011) found that they could reproduce the findings obtained by Hupbach et al. (2007) and Hupbach et al. (2009) without recourse to any new memory phenomenon such as reconsolidation. TCM assumes that the encoding of an item involves binding it to the particular context in which it is learned. According to this theory, learning Set 2 after reinstating elements of the Set 1 context with a reminder means that items from both Set 1 and Set 2 become bound to the Set 1 context. In contrast, Set 1 items are only weakly bound, if at all, to the Set 2 context. This creates an asymmetry in the contextual binding for Set 1 and Set 2 items: Whereas the Set 1 context is linked to both Set 1 and Set 2 items, the Set 2 context is linked specifically with the Set 2 items. Hence, when participants in Hupbach and colleagues studies (e.g., Hupbach et al., 2007, 2009) were prompted to recall items from Set 1 at test, reinstatement of the Set 1 context cued items from sets 1 and 2, whereas Set 2 recall prompted only the recall of Set 2 items. The delayed onset of these intrusion effects can be explained by participants having only recently learned Set 2 before short-term testing, which enables mnemonic strategies that are not available at a long-term test. When tested shortly after learning, participants can simply reject items that they know they learned just before, or which seem particularly familiar.

Beyond this conceptual explanation, Sederberg et al. (2011) performed simulations using the TCM as a basis and found that they could reproduce the findings of Hupbach et al.'s (2007) and Hupbach et al.'s (2009) experiments. Although Sederberg et al. (2011) suggest that the TCM might reflect a different (computational) level of explanation for reconsolidation-like findings, rather than a contradictory account, it does seem that reconsolidation and TCM accounts diverge theoretically. For example, Sederberg et al.'s (2011) explanation for the delayed onset of reconsolidation-like effects is very different from the idea of protein synthesis dependent cellular changes suggested by a reconsolidation-based explanation. In addition, the TCM does not suggest that memories are really modified upon reactivation, but merely become more or less easy to retrieve in the presence or absence of particular contextual cues.

Gershman, Schapiro, Hupbach, and Norman (2013) tested claims of the TCM in an fMRI-adapted version of Hupbach and colleagues' (2007) paradigm. Consistent with a TCM account, misattributions of List 2 items into List 1 were predicted by a pattern of neural activity that reflected the List 1 context prior to viewing the misattributed item. Though these results show that contextual reinstatement predicts memory errors, these results cannot rule out that this contextual reinstatement triggered a cellular reconsolidation process promoting the integration of List 2 items into the List 1 memory, as the authors themselves acknowledge. To further elucidate whether the TCM can account for findings that are currently understood in a reconsolidation framework, it would be helpful if a critical test could be conducted in humans that might falsify a reconsolidation or TCM explanation.

Despite a compelling reproduction of Hupbach and colleagues' findings (e.g., Hupbach et al., 2007, 2009), there are some factors that cannot (yet) be easily subsumed under the framework of the TCM. For example, it is unclear why particular types of reminder, such as the experimental room, induce these asymmetric effects, whereas other types, such as the experimenter, do not. However, the differential effects of reminder type are not predicted *a priori* from a reconsolidation account either. TCM might struggle to explain why only a brief reminder, but not actual recall of items, induces the asymmetric intrusion effects observed by Hupbach (2015). Reconsolidation accounts typically assume that extended memory recall does not render the memory labile (Alfei et al., 2015; Sevenster et al., 2014b), whereas one might expect that such reactivation could still result in asymmetric contextual binding.

A contextual account also presents some difficulties for early findings of Forcato and colleagues (Forcato et al., 2007, 2009). Specifically, some authors have questioned whether RIF, which is the primary outcome measure used in Forcato et al. (2007, 2009), actually reflects an inhibitory process, or even one that depends upon retrieval. The standard account of RIF argues that forgetting occurs because memories for nontarget items that are closely associated and might compete with the target are inhibited, thus aiding the recall of the target but impairing subsequent recall of the nontarget items (Anderson et al., 1994). Jonker, Seli, and Macleod (2013) suggest that findings related to RIF are better explained by a context-based account: Forgetting occurs because the experimental manipulations produce context changes that render target items less accessible. Jonker et al. (2013) found that reinstating the appropriate context under conditions that would normally result in RIF precluded RIF-like effects, and that generating unfavorable context shifts under conditions that would not normally produce RIF-like effects could induce a comparable forgetting effect.

Jonker et al.'s (2013) context-based account of RIF does not directly explain the findings of Forcato et al. (2007, 2009). However, the fact that RIF may not actually reflect an inhibitory process brought about by memory retrieval strains the use of RIF as an indirect measure with which to infer the presence of memory disruption. Hence, more direct measures of forgetting, such as retrieval errors, ought to be utilized where possible. Forcato and colleagues did use such direct assessments in studies of declarative memory enhancement (e.g., Forcato et al., 2011; Rodríguez et al., 2013), but not where memory loss/disruption was inferred.

Finally, researchers who have studied declarative memories in the context of misinformation and eyewitness testimony have also offered alternative explanations to reconsolidation-based updating or distortion of memories. Proponents of reconsolidation are not the first to have suggested that the presentation of new or misleading information can lead to changes in the original memory. For example, Loftus (1979) suggested that misleading information may "destructively update" memories, replacing old information with new. However, McCloskey and Zaragoza (1985) and Rindal et al. (2016) have highlighted several reasons why participants who receive misleading information might endorse this information instead of their original memories. Beyond mere demand characteristics, participants might favor more recent information because they did not actually encode the original information. Second, participants may remember their original learning experience, but place greater trust in the misleading information and discount their previous memory as simply incorrect. Such effects may be dependent upon reactivation, as taking a memory test could increase participants' attention to and encoding of later misinformation (Gordon & Thomas, 2014), or increase the chance that they view misleading information presented shortly afterward as corrective feedback on their responses (Rindal et al., 2016).

Specific ways of testing memories can elucidate whether such alternative explanations might account for the results of some reconsolidation-based findings, and were performed in a conceptual replication of Chan and LaPaglia (2013) by Rindal et al. (2016). Rindal et al. (2016) had participants view an initial slideshow story, and afterward reactivated some participants' memories with a brief test. Then, participants were given some misleading or nonmisleading information regarding the initial slideshow (manipulated within subjects for different items presented in the slideshow). Finally, participants underwent a memory test. Rindal et al. (2016) replicated the basic finding that reactivation can increase the endorsement of misleading information, but in a series of experiments were able to shed further light on this effect. First, participants' correct endorsement of originally seen items was not affected by whether or not they had received a reactivation before misinformation. Rather, participants appeared to be endorsing misinformation instead of giving no response, indicating that some misleading information may be accepted merely because the initial item is not remembered. Second, Rindal et al. (2016) noted that giving "true/false" responses to original items (as in Chan & LaPaglia, 2013), being asked to choose between misleading and original items, or even being asked to freely note down whether they thought they remembered items from early or later testing (the source free recognition test in Chan & LaPaglia, 2013), do not rule out the possibility that participants may still reject original items, despite having a memory for them, because they now believe those memories are false. When Rindal et al. (2016) had participants respond to a forced choice test between the originally presented item and a novel item at testing, effects of misleading information and the interaction of this with reactivation were nullified. This would suggest that participants retained their memories for the initially learned information, but may not trust this memory unless given a choice between that item and one that they are sure they do not remember.

Rindal et al. (2016) provide a convincing demonstration that the way in which memories are tested can result in very different interpretations, and that such effects may explain the results of studies such as Chan and LaPaglia (2013). However, it should be stressed that their experiments were all conducted on a single day, thus not allowing for the initial consolidation of memory, or for the reconsolidation of memory after reactivation and an intervention. A clear refutation of a reconsolidation account of retrieval-induced memory updating would also have to follow a proper reconsolidation-based design, with time allowed for initial consolidation and later reconsolidation.

What is clear, however, is that where there is evidence for the ostensible disruption or modification of memory via reconsolidation, existing studies of human declarative memory have done little to probe whether the memory trace might be easily recovered. In studies of aversive and appetitive conditioning, a range of assessments, such as reinstatement, renewal, spontaneous recovery, and testing for savings can and have been carried out to provide insight into the recoverability of memories. Neither memory recovery nor its absence can conclusively determine whether a target memory has been directly modified by an intervention. Nevertheless, one would anticipate that a genuine modification or disruption of a memory would at least render it more resistant to standard recovery procedures than its mere suppression. The persistence of purportedly reconsolidation-based effects in episodic memory could therefore be compared with that of procedures thought to produce only temporary inaccessibility, in response to attempts at memory recovery. As well as testing for the recovery of memory over time or with prompts, studies such as Rindal et al. (2016) convey how memory tests must be constructed to rule out alternative explanations.

**Summary of declarative memory reconsolidation in humans.** Table 4 provides an overview of research into declarative memory reconsolidation. In two separate reconsolidation-based paradigms with multiple experiments (object list learning and paired associate learning), independent research groups have found reactivation-dependent effects on memory, a dissociation of immediate and delayed effects, as well as time dependency of interventions. Possible boundary conditions for the induction of reconsolidation-like effects, such as the nature of memory reactivation, have also been delineated. Further studies have found evidence for memory specificity (e.g., Hupbach & Dorskind, 2014). Declarative memories assessed in a range of other paradigms also appear amenable to reactivation dependent effects of interventions. One study provided evidence consistent with all four criteria (Strange et al., 2010), though it may be noted that the time dependency of the intervention was on the order of seconds as opposed to hours, as suggested in other studies.

A meta-analysis of declarative memory studies claiming reconsolidation-based effects found that, across 34 experiments, reactivation-induced changes in memory (presumed to reflect reconsolidation) had a mean effect size of $d = 0.29$ (Scully, Napper, & Hupbach, 2016), indicating a small effect. However, the effect size for eight studies examining intrusions of interfering items into the target memory was large, at $d = 1.03$. Despite some parallels across studies regarding the importance of certain characteristics of memory reactivation, it remains a challenge to decipher exactly why these characteristics are important, how they interact with subsequent information, and whether such effects reflect the direct updating of the original memory trace or some other process. In fact, the meta-analysis of Scully, Napper, and

Table 4
*Reviewed Studies of Declarative Memory*

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Bos et al., 2014 | Word list learning | SECPT | SECPT shortly after reactivation | Yes* | — | — | — | In two experiments, reactivation + SECPT resulted in greater memory performance than reactivation + warm water (i.e., no stress), or SECPT without reactivation. No control for no reactivation + no stress precludes 2 × 2 interaction test. |
| Chan & LaPaglia, 2013 | Memory for TV episode | Misleading information | Misleading information 20 min or 48 hr after reactivation | Yes* | — | — | No | Reactivation + misinformation led to poorer memory at immediate (Experiment 3) and delayed (Experiment 6) testing. Only Experiment 6 used a 3-day design. Time dependency was tested using 20-min versus 48-hr delay between reactivation and manipulation, rather than a delayed manipulation on the same day, and used an immediate memory test rather than a three-session design. Results suggested that interfering information should be related to the original memory, indicative of memory specificity, but did not use a three-session design. |
| Coccoz, Maldonado, & Delorenzi, 2011 | Paired associate learning | CPT | CPT shortly after reactivation | Yes* | — | — | Yes | At delayed testing only, cue-reminder reactivation (but not cue-response reminder) + cold water pressor test led to enhanced memory (vs. warm water/no stress). Effects depended on specific type of reminder. Contained appropriate controls across two experiments but does not appear to include an actual 2 × 2 interaction test. |
| Dongaonkar, Hupbach, Gomez, & Nadel, 2013 | Object list learning | TSST and new learning | TSST shortly before (Experiment 1) or after (Experiment 2) reactivation and new learning | N/A | — | — | — | Pre-reactivation stress had no impact on intrusions (Experiment 1). In Experiment 2, stress after reactivation + new learning led to fewer intrusions of new learning into list 1 memory. Experiment 2 did not include no-reactivation control groups. Experiment 1 replicated reactivation dependent impact of new learning on intrusions seen in earlier object list learning studies. |
| Fernández et al., 2016 | Paired associate learning | Pavlovian conditioning | Conditioning shortly after reactivation | No | — | — | — | Declarative memories were unaffected by postreactivation Pavlovian conditioning |
| Forcato et al., 2007 | Paired associate learning | New learning | New learning 5 min, 6 hr, or 10 hr after reactivation | RD | ~Yes | — | — | Retrieval induced forgetting (RIF) was absent when List 1 memory was reactivated 5 min or 6 hr, but not 10 hr, before List 2 learning. Time dependent effects were over a larger time span than might be expected. Effects of intervention were preserved at least up to 48 hr later. Outcome variable RIF makes true control for reactivation alone or no reactivation + no intervention unfeasible. |

(*table continues*)

Table 4 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Forcato, Argibay, Pedreira, & Maldonado, 2009 | Paired associate learning | New learning | New learning 5 min after reactivation | RTD | — | — | — | Demonstrated that a cue reminder, but not a context only or cue-response reminder (allowing the participant to respond to the cue), produced the reconsolidation-like effect in retrieval-induced forgetting. |
| Forcato, Rodríguez, & Pedreira, 2011 | Paired associate learning | Single or multiple memory reactivations | Reminders separated by 5-min, 2-hr, or 24-hr intervals | RTD | ~Yes | — | Yes | Multiple cue- but not cue-response or context only reminders strengthened memory. Multiple cue reminders did not strengthen memory when separated by 24 hr, suggesting time dependency of this manipulation, but no test was done of reminders outside the reconsolidation window yet still on the same day as reactivation. Impact of cue reminders was only revealed at later testing. |
| Forcato, Fernandez, & Pedreira, 2013 | Paired associate learning | Experiment 1, single or multiple memory reactivations; Experiment 2, reactivation(s) and interfering learning | Reminders separated by 5 min. Experiment 2, Interfering learning 5 min after reminder(s) | RTD | — | — | — | Single or multiple cue reminders led to greater persistence of memory 1 week later. Multiple cue reminders also reduced the effect of interfering learning after reactivation. Effects of repeated reactivation or of interference were not observed if conducted 1 week after learning, probably due to forgetting of the original memory. |
| Gershman, Schapiro, Hupbach, & Norman, 2013 | fMRI-adapted list learning paradigm | New learning | New learning shortly after List 1 reminder | — | — | — | — | This study was not designed to demonstrate reconsolidation, but rather to test an alternative explanation. Hence, sufficient controls to demonstrate an interaction were not included. Context reinstatement as indexed in fMRI BOLD during new learning predicted whether the item would intrude at later testing. |
| Hardwicke et al., 2016 | Number or word sequence learning | New learning | New learning shortly after reactivation of old sequence | No | — | — | — | In three declarative memory interference studies, memory retrieval before new learning did not increase interference effects. |
| Hupbach, Gomez, Hardt, & Nadel, 2007 | Object list learning | New learning | New learning shortly after List 1 reminder | RD | — | — | Yes | Reactivation + new learning resulted in intrusions of newly learned material into recall of initial memory. Effects were observed at delayed but not short-term testing. |
| Hupbach, Hardt, Gomez, & Nadel, 2008 | Object list learning | New learning | New learning shortly after List 1 reminder | RTD | — | — | — | Experiments determined that a contextual reminder of initial learning was necessary and sufficient for producing intrusions of new learning into recall of old memory. |
| Hupbach, Gomez, & Nadel, 2009 | Object list learning | New learning | New learning shortly after List 1 reminder | RD | — | — | — | Follow-up of Hupbach et al., 2007, 2008. Reactivation + new learning resulted in misattribution of the source of objects from new learning as being from initial learning, but not vice versa. |

(*table continues*)

Table 4 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Hupbach, Gomez, & Nadel, 2011 | Object list learning | New learning | New learning shortly after List 1 reminder | RD | — | — | Yes | This study replicated reactivation-dependent intrusions in a sample of 5-year-olds, and showed that extra reminder cues were needed when context was overly familiar. Effects were observed at delayed but not short-term testing. |
| Hupbach & Dorskind, 2014 | Animal-object image pairing | CPT | CPT shortly after reactivation | Yes | — | Yes | — | Stress abolished the enhancement of memory brought about by reactivation in the no-stress control group. Participants served as their own "no reactivation" controls. Includes significant statistical interaction effect. |
| Hupbach, 2015 | Object list learning | New learning | New learning shortly after List 1 reminder versus Sudoku task | RTD | — | — | — | New learning hindered List 1 recall, regardless of reactivation type. Intrusions of new learning into recall of old items were dependent upon participants receiving a contextual reminder. |
| Jones, Pest, Vargas, Glisky, & Fellous, 2015 | Object list learning | New learning | New learning shortly after List 1 reminder | ~RD | — | — | — | Replicated reactivation-dependent intrusions in a young adult sample, but elderly adults showed more intrusions of newly learned material when memory was *not* reactivated. |
| Klingmüller, Caplan, & Sommer, 2017 | Object list learning | New learning | New learning shortly after List 1 reminder | ~No | — | — | — | Attempt to replicate Hupbach et al., 2007 and 2008. Failed to replicate intrusions from second list after reactivation + new learning in Experiment 1. Only with a highly salient context could a qualitative replication be observed: the impact of reactivation + new learning was less than Hupbach et al. observed. |
| Kroes, Strange, & Dolan, 2010 | Negative/neutral word list learning | Propranolol (40 mg) | Propranolol 90 min before reactivation | Yes* | — | ~Yes | No | Propranolol abolished emotional enhancement of reactivated memories, but the effects were present at reactivation, and successfully recalled emotional words were not forgotten later—opposite of the reactivation dependent effect in Strange, Kroes, Fan, & Dolan, 2010. |
| Kroes et al., 2014 | Story slideshow | ECT + general anasthesia | ECT ≈ 4 min after reactivation | Yes* | — | Yes | ~Yes | Results are consistent with a Reactivation × Manipulation interaction. Reactivation without ECT led to memory enhancement, whereas reactivation followed by ECT led to poorer performance than for nonreactivated memories. Lack of a non-ECT short-term memory test group means some effects of ECT at short-term testing cannot be ruled out, complicating the interpretation of Criterion 4. Sample was depressed patients. Used a within subjects control for reactivation. |

(*table continues*)

Table 4 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Marin, Pilgrim, & Lupien, 2010 | Story slideshow | TSST | TSST shortly after reactivation | Yes* | — | — | No | Reactivation + TSST resulted in better memory performance for emotional material than reactivation + no stress and no reactivation + stress. Effects were present at immediate and delayed testing. Did not include no reactivation + no stress group, precluding 2 × 2 ANOVA. |
| Potts & Shanks, 2012 | Paired associate learning | New learning | New learning shortly after testing of list 1 | No | — | — | — | Reactivation, by means of a full test of the original memory, reduced detrimental effects of new learning after reactivation. |
| Rodríguez et al., 2013 | Paired associate learning | Clonazepam | Clonazepam shortly after reactivation | Yes* | — | — | ~Yes | .25 mg dose of clonazepam, but not placebo or .03mg dose, after cue but not cue-response reminder, resulted in better memory performance at later testing. Differences between clonazepam and placebo were not evident at short-term test, but it could be that clonazepam prevents a decline in memory over time rather than enhancing memory after a delay. Included sufficient conditions for interaction across experiments, but a statistical test of a 2 × 2 interaction does not appear to have been performed. |
| Rubin, 1976 | Symptom reactivation | ECT + suxamethonium chloride for muscle relaxation but no general anesthesia | ECT during/shortly after reactivation | — | — | — | — | A study of obsessions, compulsions, and hallucinations, rather than declarative memory. ECT timed with symptom reactivation improved symptoms. Symptom remission ranged from 3 months to 10 years. Did not include strict reactivation or ECT controls, but patients had reactivated symptoms many times previously, and some had experienced ECT without reactivation to no effect. |
| Sandrini et al., 2013 | Modified object list learning | 1Hz rTMS to right DLPFC | rTMS 10 min after reactivation | Yes* | — | — | ~Yes | DLPFC + reactivation group had higher memory than controls at delayed but not short-term testing. Dissociation of immediate and delayed effects may reflect lack of memory loss rather than delayed memory enhancement. Did not include no reactivation + no manipulation control, precluding a 2 × 2 analysis. |
| Sandrini et al., 2014 | Modified object list learning | Anodal tDCS over left DLPFC | tDCS 10 min after reactivation | No | — | — | — | Anodal tDCS over DLPFC enhanced memory tested at both 1 and 30 days after intervention, with or without reactivation. |
| Schmidt et al., 2013 | Short movie clips | TSST and misleading information | TSST 10 min before misleading information | N/A | — | — | — | Stress induction before reactivation reduced endorsement of misinformation (but not correct responses or responses to lures) relative to no stress, but no controls to determine the need for reactivation were included. Pre-reactivation stress may affect retrieval rather than reconsolidation. |

(*table continues*)

Table 4 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Schwabe & Wolf, 2009 | Autobiographical memories | New learning | New learning shortly after reactivation | Yes | — | — | — | Statistical interaction effect indicating that neutral, but not positive or negative, autobiographical memories were impaired by learning a new story after reactivation. |
| Schwabe & Wolf, 2010 | Autobiographical memories | SECPT | SECPT 10 min after reactivation | Yes* | — | — | — | Reactivation + SECPT produced deficit in neutral but not emotional memories, relative to control conditions. Includes all appropriate control conditions but does not appear to have conducted 2 × 2 interaction test. |
| Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012 | Negative/neutral picture list learning | Propranolol (40 mg) | Propranolol 70 min before reactivation | Yes | — | — | — | Propranolol + reactivation abolished emotional enhancement of memory, demonstrated in a significant Reactivation × Manipulation interaction. |
| Schwabe, Nader, & Pruessner, 2013 | Negative/neutral picture list learning | Propranolol (40 mg) | Propranolol 60 min before reactivation | Yes | — | — | — | Propranolol + reactivation abolished emotional enhancement of memory and reduced sense of remembering, demonstrated in a significant Reactivation × Manipulation interaction. |
| Squire, Slater, & Chace, 1976 | Recent and remote memory | ECT + general anesthesia | ECT 14–18 hr or 10 min after reactivation | — | — | — | — | Reactivation shortly before ECT did not result in impaired memory. Did not include full control groups, and memory test was conducted 6 hr–10 hr after the intervention. Sample was depressed patients. |
| St. Jacques & Schacter, 2013 | Museum tour memory | Misleading images | Misleading images shortly after reactivation | — | — | — | — | Reactivation increased both recognition of correct items and endorsement of false items. Experiment used within subjects control for reactivation, but a control for the presentation of misleading images does not appear to have been used. This study did not specifically aim to test reconsolidation effects, but rather retrieval-induced changes in memory more generally. |
| Strange et al., 2010 | Word list learning | Fearful face presentation | Fearful faces interspersed throughout word retrieval task | Yes* | ~Yes | ~Yes | Yes | Memory for items preceding negative faces was impaired at delayed but not immediate testing. The effect of the manipulation was time dependent, though in the order of seconds after reactivation. Effects persisted at least up to 1 week after the intervention. Experiment 5 replicated the effects seen in Experiment 3. Planned comparisons suggest a result consistent with an interaction, but a Reactivation × Manipulation statistical test does not appear to have been performed. Successful retrieval was necessary for the impact of negative faces, suggesting effects specific to the reactivated memory, though all stimuli were reactivated as cues. |

(*table continues*)

Table 4 (*continued*)

| Authors | Paradigm | Intervention | Timing of intervention | 1 | 2 | 3 | 4 | Summary |
|---|---|---|---|---|---|---|---|---|
| Thomas, Saumier, Pitman, Tremblay, & Brunet, 2017 | Story slideshow | Propranolol (.67 mg/kg) | Propranolol shortly after, or 60 min–75 min before reactivation | — | — | — | — | Propranolol before, but not after, either initial learning or reactivation impaired memory for an emotional slideshow. No controls for reactivation were used, though lack of postretrieval propranolol effect indicates that effect of pre-reactivation propranolol cannot just be a nonspecific result of propranolol administration. |
| Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009 | Negative/neutral word list learning | Hydrocortisone (35 mg) or propranolol (80 mg) | Drug administration ≈75 min before reactivation | — | — | — | No | Cortisol, but not propranolol, was associated with reduced memory for negative and neutral items at immediate and delayed testing. No control for reactivation. This study does not appear to have aimed at testing/demonstrating reconsolidation. |
| Van Schie et al., 2017a | Picture list learning | New learning | New learning shortly after List 1 reminder | No | — | — | — | Attempted replication of Wichert, Wolf, & Schwabe, 2013b. Bayesian hypothesis testing indicated no substantial support for reactivation-dependent effects of new learning. |
| Van Schie et al., 2017b | Picture list learning | New learning | New learning shortly after List 1 reminder | No | — | — | — | Attempted replication of Wichert, Wolf, & Schwabe, 2013a. Results did not support reactivation-dependent effects, and showed no differences between strong and weak new learning. |
| Wichert et al., 2013a | Picture list learning | New learning | New learning shortly after List 1 reminder | Yes | — | — | — | Learning new items generally reduced memory sensitivity (D-prime). Impact of new learning was greatest when it was strong and preceded by reactivation. |

*Note.* 1 = Reactivation × Manipulation interaction; 2 = Time dependency; 3 = Memory specificity; 4 = Dissociation of immediate and delayed effects; — = not assessed; RD = Effects were dependent on the reactivation of the memory. Usually used where the outcome variable is dependent on there being an intervention (e.g., when intrusions from new material are the main outcome), or when reactivation alone is being studied, such that looking for a Reactivation × Manipulation interaction is not appropriate. RTD = effects were dependent upon the type of reactivation; N/A = not applicable; CPT = Cold pressor test; DLPFC = dorsolateral prefrontal cortex; ECT = electroconvulsive shock therapy; rTMS = repetitive transcranial magnetic stimulation; SECPT = Socially evaluated cold pressor test; tDCS = transcranial direct current stimulation; TSST = Trier social stress test.
~ Represents that a criterion may have been imperfectly demonstrated, or that the interpretation of this demonstration as being consistent with reconsolidation is uncertain (e.g., if observed memory impairments rapidly recover). Reasons are discussed in the summary column and in the main text. * Represents that we believe there is sufficient ground to infer a Reactivation × Manipulation interaction in a study, but that a strict 2 × 2 ANOVA with a test for an interaction was not conducted.

Hupbach (2016) failed to show that how the reactivation was performed consistently moderated later outcomes.

Studies have not always shown the anticipated reconsolidation-like effects, or consistent effects of similar experimental manipulations. As noted above, different studies have suggested that stress may either impair or enhance declarative memory, and it is not currently clear why such divergent outcomes are found. Other studies have simply failed to find any interactions between reactivation and experimental manipulations in attempted replications of earlier work. However, failure to observe reconsolidation-like effects across all paradigms tested does not invalidate findings in other paradigms if these can be convincingly attributed to reconsolidation. A key question is therefore whether there are alternative (and more parsimonious) explanations of the data that is currently taken as evidence in favor of reconsolidation in human declarative memory. Competing explanations ought to be assessed in critical tests to see if they better explain reconsolidation-like effects. It remains difficult to establish the presence of reconsolidation based on current observations in declarative memory.

## Summary of Evidence for Reconsolidation in Humans

Research into human memory reconsolidation has yielded a wealth of findings consistent with the phenomenon of reconsolidation, though the evidence base is not equal across different types of memory and paradigms studied (see Figure 1 for a graphical depiction of the evidence base provided by the studies reviewed

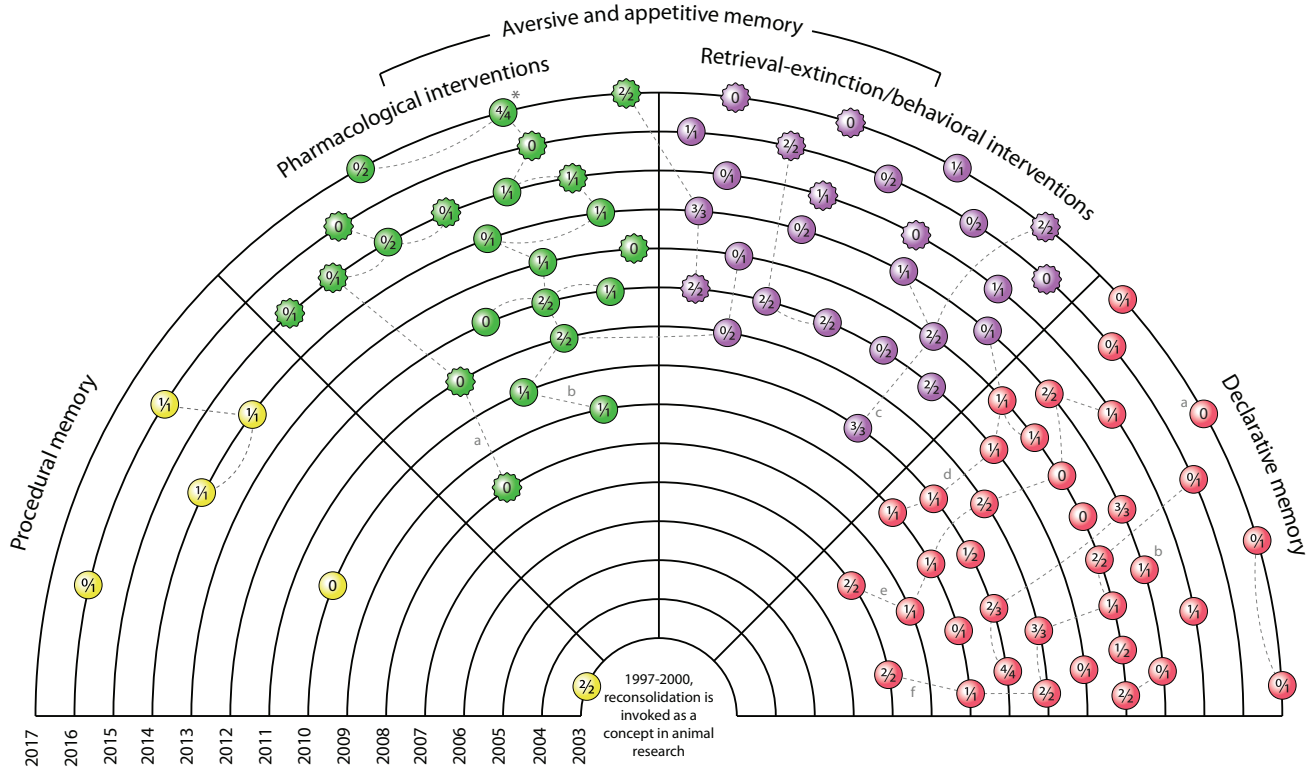


*Figure 1.* Evidence consistent with reconsolidation across different types of memory. Each circle represents a study reviewed in this paper, with numbers inside the circle reflecting the number of criteria assessed, and how many were found to be consistent with reconsolidation (e.g., 2/2 = two criteria assessed and found to be consistent with reconsolidation). For the purposes of simple representation, partial or ambiguous demonstrations of a criterion have been rated here as successful demonstrations. Studies with just a 0 may have found outcomes consistent with reconsolidation, but with insufficient controls to draw a clear conclusion, whereas those showing 0/1 or 0/2 failed to find evidence consistent with the criteria tested. Jagged circles represent studies in which a reconsolidation-based clinical intervention was performed (e.g., to reduce anxiety or craving). Studies from the same labs or primarily conducted by the same research group have been linked with dashed lines. Particularly prominent research groups in our review (4+ studies of reconsolidation) have been designated with letters: a = Pitman, Brunet and colleagues (primarily McGill University, Canada, and Harvard University, USA); b = Kindt lab, Soeter, Sevenster and colleagues (current authors, primarily University of Amsterdam, Netherlands); c = Schiller, Monfils, Phelps and colleagues (primarily New York University and University of Texas at Austin); d = Schwabe, Wolf and colleagues (primarily Ruhr University Bochum, Germany); e = Hupbach, Nadel and colleagues (primarily University of Arizona and Lehigh University, USA); f = Forcato, Pedreira and colleagues (primarily University of Buenos Aires, Argentina). * = this study was submitted for publication in mid 2017, but the final publication will be Kindt & Soeter, 2018. See the online article for the color version of this figure.

here). For procedural memory, one early study produced findings consistent with a Reactivation × Manipulation interaction and a dissociation of immediate and delayed effects. However, only a small amount of further research seems to have been conducted assessing reconsolidation of procedural memory, and studies that have been done have not been able to clearly corroborate these initial findings.

For aversive memories, research using propranolol to neutralize subsequent emotional memory expression has provided evidence that aligns with all of the suggested reconsolidation criteria. Retrieval-extinction procedures have also provided results consistent with a Reactivation × Manipulation interaction, time dependency of effects, and memory specificity, though we are not aware of any tests of a dissociation between immediate and delayed effects in humans. Notably, studies of both these interventions have often included established tests of memory recovery, thus providing further insight into the durability of such effects. Research into possible clinical applications of these approaches for both anxiety-related and addiction-related disorders is in its early stages, but shows considerable promise. Both paradigms have also had some failed replications. Studies of appetitive memory in humans are in their early stages, but both pharmacological and retrieval-extinction approaches have provided evidence consistent with a Reactivation × Manipulation interaction, and time dependency of the interventions.

Declarative memory research has expanded to encompass a range of different paradigms and interventions. We are unaware of any study that has found results unambiguously consistent with all the criteria we propose, but across declarative memory research as a whole researchers have found evidence consistent with Reactivation × Manipulation interactions, time dependency, memory specificity, and a dissociation of immediate and delayed effects. One study found results consistent with all reconsolidation criteria (Strange et al., 2010), though with time dependency of the intervention in the order of seconds. Given the host of different experimental tasks and manipulations used, it should not be assumed that the presence (or absence) of results consistent with criteria in one study can be used to support the idea of reconsolidation in a different experimental paradigm of the same memory type.

As stressed earlier, one cannot make strong inferences as to the presence of an unobserved neurobiological process based on such behavioral observations. Indeed, we have discussed a range of alternative explanations for these observations across the different paradigms and types of memory studied. In addition, while we have discussed in the greatest detail what we believe to be the most prominent, influential, and/or well-developed examples of reconsolidation-based research, we have also highlighted several inconsistent findings or failures to observe any reconsolidation-like effects. However, failed replications or null results from individual studies in a particular paradigm or memory type should not be taken as evidence against the idea of reconsolidation in humans *per se* if convincing findings exist in other domains.

There are limitations to the current evidence base regarding reconsolidation. In reviewing studies, we found that only a small minority provided a direct statistical test of a Reactivation × Manipulation interaction, with many studies not including a control group receiving neither reactivation nor any manipulation, or not performing a statistical interaction test when the appropriate control conditions were utilized. In a number of cases, it nevertheless seems reasonable to infer the presence of a Reactivation × Manipulation interaction. For example, in studies of fear conditioning, experiments using within group controls for no reactivation and no manipulation (e.g., Soeter & Kindt, 2011) indicate that it is quite implausible for the effects of propranolol + reactivation on the attenuation of startle responses to be explained by summing the effects of each in isolation (i.e., the control conditions do not produce any attenuation of the fear response), even though such studies have not always included a no reactivation + no manipulation control group in order to clearly demonstrate this. Similarly, retrieval-extinction studies have often used extinction outside the reconsolidation window as a control for the potential additive effects of reactivation + extinction, without including separate control groups. Certainly, reconsolidation-based research does not always need to include the full range of control conditions for determining an interaction. There are many interesting questions inspired by the idea of reconsolidation beyond just whether it can be proven to occur. Especially once an effect has been established, researchers will likely aim to determine necessary and sufficient conditions for inducing it, at which point so many control groups may be inefficient given the research question. However, where novel paradigms are used, or where effects of an intervention are subtle or inconsistent, it can be more difficult to determine whether an interaction effect is likely the best explanation for an observed outcome.

It is also apparent that most of the criteria commonly go unassessed. Whether a study or series of studies includes tests of all criteria will depend on the research question, but the most convincing demonstrations of reconsolidation are likely to result from all criteria being demonstrated within particular paradigms, if not in a single study, rather than multiple incomplete demonstrations across disparate research lines. Finally, where reconsolidation-like effects are observed, the degree to which these effects are sustained and resistant to attempts at memory recovery often goes untested. The following section discusses the durability of reactivation-dependent modifications of memory as a possible further criterion for demonstrating memory reconsolidation.

## Long-Term Effects of Reconsolidation-Based Interventions and the Storage Versus Retrieval Debate

In addition to the four-part framework we have suggested, it is worth considering a further possible criterion that might be taken as suggestive of reconsolidation: the durability of reactivation-dependent modifications of memory. Long-lasting effects are usually seen to be consistent with a reconsolidation-induced modification of the original memory trace, whereas the capacity to retrieve a supposedly disrupted or modified memory trace is typically seen as evidence in favor of a temporary deficit in retrieval, without any actual change to the reactivated memory trace.

Relatively long-term follow-ups have been conducted for both pharmacological disruption and retrieval-extinction procedures, ranging from 1 month to 1 and a half years (Björkstrand et al., 2016, 2017; Schiller et al., 2010; Soeter & Kindt, 2010, 2015a). From such findings, it can be argued that the observed reductions in fear responding are unlikely to be the result of simple extinction, which is often reversed after reinstatement and tends to show spontaneous recovery. However, a recurring theme in memory

research is that a failure to observe the expression of a memory is not synonymous with memory loss. It is always possible that continued testing or a different type of retrieval cue could produce retrieval, meaning that we cannot infer memory loss from the absence of memory expression. In short, there is no behavioral assay that can firmly establish memory loss, or indeed the direct modification of a memory trace.

In animal research, investigators have used invasive procedures to provide evidence for memory storage failure (i.e., memory loss), rather than retrieval failure, as a result of reconsolidation blockade. For example, Hardt, Wang, and Nader (2009) drew upon previous research demonstrating that the N-methyl-D-aspartate receptors (NMDAr) were necessary only when contextual fear conditioning was acquired for the first, but not the second time (Bannerman, Good, Butcher, Ramsay, & Morris, 1995; Sanders & Fanselow, 2003), and confirmed this in their own experiment. Hardt et al. (2009) went on to show that blocking the reconsolidation of a contextual fear memory with anisomycin returned the animal to an essentially naïve state: After reconsolidation disruption, the NMDArs were again required for contextual fear conditioning, just as if animals were learning for the first time. These findings were taken to suggest a failure of memory storage in this experimental model.

Yet, even with very specific neurobiological markers, interpretation is not straightforward. It might be argued that the lack of need for NMDAr activation for a second learning event is due to the original memory being retrieved in some way and supporting new learning on the second task (Matzel & Miller, 2009). Hence, the renewed need for NMDAr activation after a reconsolidation-based amnestic procedure could again be attributed to a retrieval failure caused by the intervention. If we interpret the findings of Hardt and colleagues as a clear refutation of retrieval failure, then we should still be reserved in the extent to which we assume this applies to studies of reconsolidation outside of pharmacological interventions for fear-conditioning. Just as challenges to the reconsolidation account from null findings or alternative explanations in particular paradigms should not be seen as invalidating the entire spectrum of reconsolidation research, neither should the implications of findings such as Hardt et al. (2009) be unreasonably extended to all the diverse lines of research claiming to demonstrate reconsolidation effects.

Difficulties such as these can be especially problematic for human research because the extent of invasive procedures that can be carried out in human samples is limited. Standard neuroimaging techniques such as fMRI may show differences between groups as a result of experimental memory manipulations, but these are unlikely to be as specific as the presence of established neurobiological markers of new learning. Moreover, the types of declarative and episodic memories often studied in human reconsolidation research do not always have clear parallels in animal models in which more precise neurobiological assessments might be made. This can preclude the highly informative translation of findings from lower levels of analysis that has proven so fruitful in research on anxiety and fear (e.g., Debiec & LeDoux, 2004 informing Kindt et al., 2009, or Monfils et al., 2009 providing impetus for Schiller et al., 2010).

It is promising, however, that advances are being made in this direction. Jones, Bukoski, Nadel, and Fellous (2012) have devised an appetitive spatial memory task for rats aimed at modeling reconsolidation-based research on human list learning (e.g., Hupbach et al., 2007). Jones et al. (2012) found striking parallels (as well as some inconsistencies) between the intrusions rats display from learning different spatial tasks and the intrusions humans display from learning different lists of objects. Such animal models could help elucidate the neurobiological underpinnings of declarative memory updating effects.

Just as an absence of memory expression is not synonymous with memory loss, it should also be stressed that later memory retrieval is not invariably proof that a memory trace was not disrupted or modified by a process of reconsolidation. Advocates of a reconsolidation account are not restricted to the view that the entire memory trace is eliminated or fails to be stored altogether following the disruption of reconsolidation. Dissociations between response systems after propranolol delivered so as to interfere with reconsolidation clearly show that only part of the memory is affected by such manipulations (Soeter & Kindt, 2010). Likewise, after a reconsolidation-based intervention to diminish fear of real-life spiders, participants did not forget that they were previously afraid of spiders, nor did they display a complete absence of fear responding (Soeter & Kindt, 2015a). Hence, even if a memory trace is really modified via reconsolidation, parts of the trace that are retained could prove sufficient for memory retrieval, or facilitate the formation of a new memory, the behavioral expression of which is very similar to the original. It would be surprising indeed if such short interventions could entirely eliminate all the cellular changes that support long-term memory, and some optogenetic research in fact suggests that protein synthesis independent changes in neuronal networks may be maintained even after blockade of initial memory consolidation (Kitamura et al., 2017).

Although the presence or absence of memory recovery cannot be seen as a refutation or proof of memory updating or disruption, probing memories using various established approaches—such as testing for spontaneous recovery, reinstatement, renewal, and rapid reacquisition—can still provide valuable insights. Disrupted memories may not be irretrievable, but if human studies are to parallel animal research demonstrating reconsolidation, then one would expect modified memories to be more resistant to such procedures than, for example, memories affected by standard extinction. In declarative memory, the exact procedures used in fear conditioning may not be applicable, but researchers can seek to probe the robustness of their interventions by giving reminders, and can also test alternative explanations by designing tests of memory to preclude such factors as memories being present but not trusted (cf., McCloskey & Zaragoza, 1985; Rindal et al., 2016). While such memory tests have been quite frequent in studies of fear conditioning, comparable tests in declarative memory are rare. In each table, we have aimed to highlight where long-term tests of memory, or other means of probing memory recovery, have been used.

## Conclusion

Studies in humans have produced a range of findings consistent with the phenomenon of memory reconsolidation. Most promisingly, these research programs are bridging the gap not just between animal models and humans, but also between experimental studies and clinical interventions. There is evidence for Reactivation × Manipulation interactions, time dependency, memory spec-

ificity, and the dissociation of immediate and delayed effects, in human studies. These observations are consistent with findings taken to reflect reconsolidation in animal models (Dudai, 2006; Nader & Hardt, 2009; Tronson & Taylor, 2007), and support the idea that reactivation can induce a transient, unstable state in a previously consolidated memory, during which the memory might be modified or disrupted, and requiring a process of restabilization in order to persist.

However, it is not possible to conclusively infer the presence of a specific neurobiological process based on current behavioral or neuroimaging data. A number of inconsistent findings in the literature remain, and not all reconsolidation criteria have been assessed in the different paradigms used. Additionally, the production of irreversible changes in memories may not be a hallmark of reconsolidation, as proponents of a reconsolidation account are not restricted to the assumption that a memory trace is entirely erased by a reconsolidation-based procedure. These caveats may temper the enthusiasm with which reconsolidation has been received. Nevertheless, we would argue that reconsolidation has provided a framework within which a range of new experimental manipulations and clinical interventions have been formulated and tested. Such investigations have already produced surprising and clinically relevant findings. We are not aware of any a priori hypotheses, besides reconsolidation, that would have predicted such results, and compelled researchers to investigate them.

Evidently, there are many opportunities for informative translational research in the field of reconsolidation. Research into reconsolidation may have many implications beyond just informing our theoretical understanding of memory function, be it in terms of understanding how memories can be molded in light of new and even misleading information—with potential importance in legal settings—to how pathological emotional memories may be modified, with clear implications for novel treatments. It should be stressed that if, as we believe, the greatest prospect for reconsolidation in humans is its potential to unlock new approaches to the treatment of psychiatric disorders, then the goal of translational research should not merely be the production of more translational research, but the actual development of effective clinical treatments. At some point, exponents of experimental models claiming clinical relevance must aim to demonstrate this in trials of clinical efficacy. Experimental studies of reconsolidation should be purposely geared toward answering clinically relevant questions, and where reconsolidation is claimed as a mechanism, studies should be designed so as to be able to evaluate this possibility from the start. Work in clinical populations should also be pursued to counter some of the limitations of typical experimental studies, such as the highly controlled learning histories of participants, as well as the significance and age of the targeted memories.

If clinical utility is the ultimate aim of such research, then it ought not to be considered a resounding failure for proponents of reconsolidation if alternative explanations for findings are available. The clinical utility of a reconsolidation-based procedure does not necessarily stand or fall on whether or not it represents a definitive demonstration of reconsolidation, but on whether it can produce the desired outcome: effectively alleviating the burden of mental illness. Yet, a mechanistic understanding of what is occurring in such interventions is essential. As McNally (2007, p. 751) has urged: "Theoretical agnosticism about mediating mechanisms is acceptable only when treatment works with flawless fidelity." Advocates of experimental psychopathology (e.g., Forsyth & Zvolensky, 2001) and evidence-based practice more generally (e.g., Roth & Fonagy, 2013; Wampold & Imel, 2015) have recognized this for some time, and an understanding of the mechanisms underpinning psychiatric problems and their resolution is now highlighted in the Research Domain Criteria of the National Institute of Mental Health (e.g., Sanislow et al., 2010). A more complete understanding of how and why effective treatments work can facilitate their optimization, highlight superfluous elements of an intervention to increase efficiency, and help determine what approaches will work for whom, and why (cf., Forsyth & Zvolensky, 2001; Roth & Fonagy, 2013; Sanislow et al., 2010; Wampold & Imel, 2015).

Premature appeals to the phenomenon of reconsolidation as a candidate mechanism for a treatment are unlikely to advance the field or aid in realizing the clinical potential of reconsolidation. Expanding the concept of reconsolidation so broadly as to function as an explanation for the efficacy of any number of clinical interventions or experimental findings that involve memory reactivation may render the concept so broadly applicable as to be effectively meaningless. Reconsolidation is an exciting clinical prospect precisely because it suggests *new* ways of treating mental disorders, and harnessing this potential ought to involve more than reinterpreting existing interventions as already involving reconsolidation. Hence, invocations of reconsolidation as an explanation for treatment effects or experimental findings should not simply be made post hoc as a tantalizing yet improperly assessed possibility, but based upon studies purposely designed within a framework for demonstrating reconsolidation-like effects.

Ethical and practical concerns may limit the demonstration of all the criteria we suggest in clinical samples, as this would require a number of inactive conditions that could be deemed unacceptable in severe cases of mental illness. However, clinical studies can be grounded in a supporting body of experimental research investigating the same intervention in sub- or nonclinical participants. Lines of research demonstrating a Reactivation × Manipulation interaction, time-dependency of the manipulation, memory specificity, and a dissociation of immediate and delayed effects, as well as having provided evidence in favor of reconsolidation over alternative explanations, will provide the most convincing demonstrations of reconsolidation. With careful and critically considered research, the concept of reconsolidation can be used to formulate and test powerful new treatments, translating developments from the lab to the clinic.

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