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A paradigm shift in the treatment of emotional memory disorders: Lessons from basic science

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ABSTRACT

Experiments demonstrating post-reactivation amnesia for learned fear in animals have generated a novel and influential hypothesis on the plasticity of memory, usually referred to as *memory reconsolidation.* The clinical potential of pharmacologically disrupting the process of memory reconsolidation has sparked a wave of interest into whether this phenomenon can also be demonstrated in humans, and ultimately harnessed for therapeutic purposes. In this essay we outline how the work of Karim Nader and colleagues has moved the field forward from a focus on extinction learning to the prospect of disrupting memory reconsolidation. We then review some promising findings on the necessary conditions, as well as potential boundary conditions, of pharmacologically disrupting the process of memory reconsolidation obtained in our laboratory. Even though laboratory experiments in animals and humans suggest that we may be at the brink of a breakthrough in fundamentally changing emotional memories, the necessary and sufficient conditions for targeting and disrupting memory reconsolidation in clinical practice are largely unknown. There is likely no universally effective reactivation procedure for triggering the reconsolidation of clinically significant emotional memories, and the impact of subtle boundary conditions observed in basic experiments compounds this issue. Notwithstanding these challenges, the discovery of changing emotional memory through disrupting the process of memory reconsolidation has unquestionably invigorated the field.

1. Introduction

While it may be adaptive to have strong memories for the most important events in life, the resistance of emotional memory to change can also be harmful. People suffering from posttraumatic stress disorder (PTSD) can be so plagued by their memories as to be constantly vigilant, with vivid intrusions provoked by even tangential reminders of their trauma. Patients with a specific phobia may have such strong emotional reactions to particular stimuli that they build their lives around their avoidance. Several epidemiological studies confirm that anxiety and trauma-related disorders – which we argue can be understood at least in part as disorders of emotional memory (Kindt, 2014) – are the most prevalent psychiatric conditions and among the most impairing chronic diseases in Europe (Wittchen and Jacobi, 2005) and the United States (Kessler et al., 2005). Since the end of the nineteenth century, dozens of pharmacological and psychological treatments have been developed with the aim of changing excessively strong emotional memories and their undesired effects. Although great advances have been made over the last decades, even the most effective contemporary treatments are thought to only dampen or inhibit emotional responding, leaving the original pathological memory intact (Bouton, 2002). Consequently, when patients initially benefit from treatment, relapse is frustratingly common (Craske et al., 2014; Hofmann and Smits, 2008; Loerinc et al., 2015). The scale of mental health difficulties and the shortcomings of existing treatments call for a better understanding of therapeutic forgetting. In this essay we illustrate how the basic principles of learning and memory are indispensable in understanding the modification of emotional memory, paving the way for the development of revolutionary treatment approaches for people suffering from fear and anxiety disorders.

A major breakthrough in neuroscience was achieved two decades ago, with the discovery that emotional memories are not as indelible as once thought,[1] and can be modified after recall (Przybyslawski et al., 1999; Nader et al., 2000). In a series of landmark experiments in rats,

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[1] This may arguably be deemed a rediscovery, as Donald Lewis and others had investigated post-retrieval amnesia in the 1960 s

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Nader and colleagues found that retrieval of consolidated fear memories could render them vulnerable to disruption (i.e., destabilized), with reactivated memories apparently requiring *de novo* protein synthesis to be retained. This process, now known as 'memory reconsolidation', opens the possibility of targeting emotional memories with amnesic agents. Since these seminal studies in animal models, evidence for pharmacologically induced amnesia for fear has progressed from laboratory studies in animals to experimental and even clinical work in humans (Elsey et al., 2018; Kindt, 2018).

2. Karim's shoulders

The observation of post-retrieval amnesia for learned fear in animals stimulated a new research program at the University of Amsterdam led by the lead author of this essay, with the aim of testing whether the process of fear memory reconsolidation could be disrupted in humans as well. If we were able to observe a similar post-retrieval amnesia for learned fear in humans, then this new approach could remedy the problem of relapse in patients suffering from maladaptive emotional memories. The ability to rapidly attenuate the impact of horrific or otherwise undesirable memories – possibly even with a single session intervention – would represent a game-changing shift in the treatment of mental illness. Currently, most therapies aim to produce a gradual diminution of fear through repeated sessions (or single, longer sessions) in which patients are expected to slowly develop the capabilities to regulate or learn new ways of thinking about their fears. In many cases the fear remains at a lower level or even returns (Craske et al., 2014). With a successful reconsolidation-based procedure, abrupt and profound reductions in fear may be realised in a single, relatively brief, treatment session. Such a treatment would also be distinct from the current use of pharmacological agents for fear reduction, with possibly as little as a single drug administration during a specific time window around memory reactivation, so as to interfere with a specific process and target a particular memory. This is in sharp contrast to typical pharmacological approaches, which involve repeated drug intake to produce a general reduction in fear (Farach et al., 2012; Baldwin et al., 2014; Jakubovski et al., 2019).

Most studies on post-retrieval amnesia in animal models utilize a range of potentially neurotoxic drugs and means of delivery that are not feasible in humans subjects, such as anisomycin delivered directly to the amygdala (Finnie and Nader, 2012). However, when we designed our first experiment in 2008 (Kindt et al., 2009), some animal researchers had also induced post-reactivation amnesia with the β-adrenergic receptor (β-AR) antagonist propranolol, which produced amnesic effects both when delivered systemically or directly into the amygdala (Przybyslawski et al., 1999; Dębiec and Ledoux, 2004). For β-ARs, it has been demonstrated that they have an essential role in protein synthesis required for both memory consolidation and reconsolidation (Johansen et al., 2014; Otis et al., 2015). As a non-toxic and commonly used off-label medication with the capacity to cross the blood-brain barrier, propranolol was viable for experimental work on reconsolidation in humans. We found that a single 40 mg dose of propranolol, administered *prior to* or *shortly after* memory reactivation, neutralised fear-conditioned startle responses to conditioned stimuli, and prevented the return of fear up to at least one month later (see Elsey et al., 2018; Elsey and Kindt, 2017a, 2017b; Kindt, 2018 for reviews). Whereas spontaneous recovery, renewal, reinstatement, and rapid reacquisition typically occur if a fear memory is simply extinguished, we found that memories treated with this reconsolidation-based approach were not susceptible to such retrieval techniques. The pharmacological induction of post-retrieval amnesia thus appears to induce more lasting reductions in fear memory expression than extinction.

3. Targeting the affective value of memory instead of threat expectancies

Interestingly, disrupting reconsolidation with the ß-adrenergic blocker propranolol exclusively dampened the startle response and distress ratings, while leaving the explicit expectation of threat (i.e., contingency awareness) (Kindt et al., 2009) and electrodermal activity intact (Soeter and Kindt, 2010, 2011; Sevenster et al., 2012). Hence, it is believed that the pharmacological manipulation of memory reconsolidation directly reduces the emotional valence attributed to the conditioned threat stimulus (CS), while the declarative memory of the conditioning experience and concordant predictive properties of the CS remain unaffected. A more recent and elegant study in animals corroborated our observations in humans by parsing the predictive vs. the emotional/motivational components of a memory in a Pavlovian-conditioned approach task (Cogan et al., 2018). Post-reactivation propranolol was found to blunt the emotional/motivational impact of the CS, while leaving the association between the conditioned and unconditioned stimulus (CS->US) itself intact: animals were seen to attend to or approach regions where reward could be predicted, but were not motivated to fully engage, just as humans in our experiments appeared to recollect their conditioning experiences, but did not display defensive behaviour to formerly aversive cues. This reconsolidation-based intervention thus contrasts strongly with the most well-established treatments for anxiety and trauma-related disorders, namely Exposure Therapy and Cognitive Behavioural Therapy (CBT). A central tenet of many contemporary accounts of Exposure and CBT is that a change in cognitive processes, such as predictive properties of a stimulus and threat expectations (i.e., expectancy violations), precede and account for the effect of treatment on emotional responses (Hofmann et al., 2013; Craske et al., 2014). In contrast to this cognitive mediation hypothesis, an initial cognitive change seems not to be required for the current reconsolidation intervention. In fact, evidence thus far suggests that when a significant change in expectations is reported upon reactivation, it may even preclude the induction of reconsolidation (Bos et al., 2012; Sevenster et al., 2014).

3.1. *Memory specific fear dampening generalizes across stimuli of the same semantic category*

Over the past decade, we have addressed several other issues of both clinical and theoretical relevance, before translating this reconsolidation-based intervention to clinical and subclinical populations. If such an approach is to be used in patients with anxiety disorders, then the intervention should yield reasonably precise modifications of targeted memories, as opposed to a general fear-dampening effect. At the same time, if disrupting memory reconsolidation has clinical potential, the fear-reducing effect should not be so circumscribed as to be restricted to the reactivation stimulus alone: generalisation of fears to category-related stimuli is common in anxiety disorders (e.g., fearing shepherd dogs, bulldogs, and terriers, rather than just one type of dog), and so generalisation of fear reductions is also desirable. In several studies we induced two different fear associations (CS1 -> US, CS2 -> US), in which two pictures of distinct semantic categories were associated with the same aversive outcome (i.e., an electrical stimulus or US). We demonstrated that propranolol selectively neutralised fear-potentiated startle to a CS1 that was reactivated, leaving responses to the non-reactivated CS2 intact (Soeter and Kindt, 2011, 2012a; Kindt and Soeter, 2018). These findings suggest that the reconsolidation intervention can be used to selectively target a specific fear, rather than producing a general (and probably undesirable) dampening of fear. Furthermore, the fear neutralisation was found to extend beyond the reactivated cue to stimuli within the same semantic category (Soeter and Kindt, 2011, 2012a). Hence, pharmacologically disrupting the process of memory reconsolidation is not only markedly different to dominant psychotherapeutic approaches, but also stands in contrast to

traditional pharmacological interventions (Elsey and Kindt, 2016; Kindt, 2018): The drug is only administered once, within a particular time window upon memory reactivation, and it neutralizes a specific fear. The extension of effects beyond the reactivated stimulus also highlights the clinical potential of this approach, and further suggests a possible superiority to approaches based upon the inhibition of the target memory (i.e., extinction learning), which often require training in multiple contexts or with many category exemplars presented in different contexts to achieve a generalised effect (Lipp et al., 2020; Craske et al., 2022).

In addition to assessing whether the fear-reducing effect of reactivation + propranolol generalizes to cues from the same semantic category, we tested whether it was possible to induce and disrupt reconsolidation using a reactivation cue that was not exactly the same as that used during initial learning. Most studies of memory reconsolidation have utilized the originally learned CS as the reactivation cue (Finnie and Nader, 2012; Elsey et al., 2018). For anxiety disorders, or indeed any memory formed outside of the lab, it is rarely clear which specific cues might be central to the underlying fear memory, or even what the initial learning events were, as fear may result not only from direct experience, but also from vicarious experience, information, imagination, or other more passive means of learning that the patient cannot recall. Even direct experiences may be so far in the past as to be only dimly remembered, if at all. If reconsolidation could only be induced with the use of cues that exactly match the initial encoding, then it would have little translational potential. We found that an abstract cue (e.g., the word 'spider') could trigger reconsolidation for a fear memory in which the initial learning experience was pairing an electric shock with a visual cue (e.g., a picture of a spider) (Soeter and Kindt, 2015a). This finding is promising for clinical translation, as it suggests that precise knowledge of some kind of hypothesised, but largely intangible initial learning experience may not be necessary for a successful neutralisation of fear. On the other hand, not all cues related to the original fear memory (CS -> US) will trigger memory reconsolidation. In a second-order fear-conditioning study in animals (CS1 -> US, CS2 -> CS1), the indirectly associated cue (i.e., second-order conditioned stimulus, CS2) failed to induce reconsolidation of the initially learned fear memory (first-order conditioned stimulus, CS1 -> US; Dębiec et al., 2006). In contrast, reactivation of the first-order cue combined with an amnesic intervention could produce fear neutralisation for the second-order cue (Dębiec et al., 2006). It would thus seem that although an exact replica of the initial learning experience is not necessary for triggering reconsolidation, the retrieval cue should at least be directly related to the US.

3.2. Necessary conditions to trigger memory reconsolidation

In the past two decades there have been many experimental findings consistent with memory reconsolidation from organisms as diverse as crabs to snails, honeybees to humans, using a wide range of learning tasks and amnesic agents (Elsey et al., 2018; Finnie and Nader, 2012). These findings may be taken to suggest that reconsolidation is a fundamental process in learning and memory. Despite the plethora of findings that align with reconsolidation, it is not the case that reconsolidation always occurs, or that it is easy to induce. For instance, over the years we have seen several failed replications of the basic memory reconsolidation effect in humans, while we used a very similar fear-conditioning procedure (Bos et al., 2014; Schroyens et al., 2017; Chalkia et al., 2019; Stemerding et al., 2022). Even though we have no straightforward explanation for the absence of memory reconsolidation, it is noteworthy that fear extinction was not observed in these studies either. This may indicate that the fear memory in the failed replication studies may have been too strong to be destabilized by the usual reactivation procedure. Many experimental conditions involving memory reactivation clearly do not trigger the process of memory reconsolidation. Evidence for boundary conditions has typically been based on failures to produce amnesic effects using a single reactivation procedure (Milekic and Alberini, 2002). Yet, it is unlikely that there would be a single means of reactivation that is universally effective in producing reconsolidation (Finnie and Nader, 2012; Faliagkas et al., 2018). For instance, some research has suggested that remote or strongly trained memories that appear to be resistant to disruption may be rendered vulnerable with the use of more extended reactivation sessions (Suzuki et al., 2004; Frankland et al., 2006), by adding novel elements during reactivation (Winters et al., 2009), or by changing the temporal relationship between the CS and US (Díaz-Mataix et al., 2013). Furthermore, simply attempting to disrupt the reconsolidation of strongly trained memories at more remote time points may be effective (Robinson and Franklin, 2010; Wang et al., 2009). Our own work with clinical patients also serves as a proof of principle that exceptionally strong fear memories may be targeted with reconsolidation-based approaches, though controlled trials are necessary to more firmly establish this. Hence, an alternative hypothesis is that strict boundary conditions do not exist. Memories may change over time and are likely to vary considerably depending on the learning experiences that feed into them, meaning that different means of reactivation may be necessary to trigger reconsolidation depending upon these factors, but that boundary conditions are relative rather than absolute. This fits with the idea that reconsolidation may be an adaptive mechanism that keeps memories up to date (Dudai, 2009) – precisely what information is deemed relevant or important may be dependent upon the content and strength of initial training, the current context, as well as how long ago it occurred. Reconsolidation may even be induced when essentially repeated training trials are given, so long as there is some discrepancy between what has already been learned and what can be learned from the current situation (Pedreira et al., 2004; Morris et al., 2006: Merlo et al., 2014; Sevenster et al., 2014). This construct, dubbed 'Prediction Error' (PE) (cf. Rescorla and Wagner, 1972), has since been leveraged in several experimental settings and across different species to trigger reconsolidation. In case of a fully reinforced and asymptotic learning curve, omission of a predicted reinforcement during memory reactivation (i.e., negative PE) may trigger the process of reconsolidation (Waelti, Dickinson and Schultz, 2001), while a reinforced reactivation trial would probably leave the memory unaffected. In contrast, if memory reactivation follows a partially reinforced, non-asymptotic learning experience, a similar reinforcement trial (i.e., positive PE) would prompt some additional learning and should therefore be capable to destabilize the memory trace.

In our *human* studies, propranolol (timed to interfere with post-reactivation reconsolidation) was found to selectively impact upon the emotional expression of fear memory (i.e., fear potentiated startle response), leaving the explicit expression of learned contingencies (i.e., US-expectancy ratings) intact (Kindt et al., 2009; Sevenster et al., 2012; Soeter and Kindt, 2010, 2011). It was therefore possible to develop a measure of PE through the expression of the declarative memory – which was unaffected by the reconsolidation-based intervention – to potentially predict whether reconsolidation did or did not occur (Sevenster et al., 2013, 2014). We found that reconsolidation of a human fear-conditioning memory was most reliably triggered by reactivations that elicited a small change in US expectancy ratings the following day. More specifically, reconsolidation could be triggered both when there was a positive PE (reinforcement occurred when it was not expected) or a negative PE (reinforcement did not occur when it was expected). Such conditions resulted in a small updating of the explicit threat expectancy. Reactivations that did not result in a change of reported US expectancies typically did not produce amnesia, despite there having been both a memory reactivation and administration of propranolol. Although such findings offer important insights into the optimal conditions for inducing reconsolidation, several challenges must still be overcome for the translation of memory reconsolidation to clinical practice.

Firstly, while PE might be a necessary condition for triggering memory reconsolidation, it is not sufficient. Depending on the

magnitude of PE, reactivation may give rise to the formation of new memories (i.e., inhibitory learning/extinction). Multiple studies suggest that the induction of extinction may preclude the induction of reconsolidation from the same reactivation event (Bos et al., 2012; Eisenberg et al., 2003; Lee et al., 2006). When reactivation involves the repeated or extended presentation of unreinforced CSs, the increased magnitude of PE may eventually reduce both the threat expectancy and fear response. Rather than triggering reconsolidation, computational approaches suggest that excessive prediction error may lead to the inference of a different 'latent cause' of the observed experiences (Gershman et al., 2017). In essence, when faced with too great a violation of expectations after several unreinforced CS presentations, the experimental subject consciously or unconsciously infers that the causal process producing the observed outcomes is not the same as it was during initial learning, and so they generate a new memory for this new cause, leaving the initial memory intact.

Even before reductions in fear responding can be observed at a physiological level, it is possible that boundary conditions for memory reconsolidation have already been reached (Sevenster et al., 2014). Although successful induction of memory reconsolidation was found to be marked by a slight updating of expectancies on the subsequent day (Sevenster et al., 2013, 2014), we also found that a decrease in threat expectancy already during reconsolidation, or too much uncertainty with respect to the occurrence of the expected threat (i.e., US) (Gerlicher, Verweij and Kindt, 2022) prevented the induction of amnesia by post-reactivation propranolol. Such shifts in expectancy may demarcate the boundary between reactivations that will or will not result in reconsolidation, extinction, or mere retrieval.

Studies in both humans and animal models have indicated that reconsolidation and extinction may also be separated by a transitional stage – referred to as the 'limbo' state – during which neither reconsolidation nor extinction are triggered (Merlo et al., 2014). Amnestic agents administered during limbo affect neither reconsolidation nor extinction. Hence, a picture begins to appear of a very fine balancing act, in which too little prediction error from a reactivation trial may produce mere retrieval, but too much predicton error risks inducing limbo or extinction. Clearly this poses a challenge to the translational feasibility of reconsolidation-based interventions in clinical practice, where the optimum reactivation conditions are even more difficult to determine than in well-controlled fear-conditioning studies. In these laboratory studies, the initial learning experiences of participants can be carefully controlled, such that although there are individual differences among participants, at least their learning history can be accounted for. As noted previously, individuals with anxiety disorders have arrived at their current state through myriad paths, and so one must consider not only a generically most appropriate means of reactivation, but also the possibility that this varies greatly among patients.

One way through which these difficulties might be alleviated would be if it were possible to develop a real-time marker of PE, or some other process, that might predict the successful induction of reconsolidation. The aforementioned index of PE used in experimental studies (Sevenster et al., 2013) is limited by the fact that it is only revealed upon a subsequent day, and thus cannot be utilised as a means of determining when one should put a stop to memory reactivation. Ideally, a real-time marker – cognitive, physiological, or neurobiological – for whether reconsolidation was likely to be triggered by a particular reactivation could be consulted during reactivation, so that the experimenter or clinician knows when reactivation is most likely to have been sufficient. Future research from our lab aims to investigate whether such a real-time marker of successful reactivation can be developed. With such a tool, reactivation sessions could be adapted in real time, with the clinician determining whether an exposure task should be prolonged or terminated. This is, however, likely to be a difficult (if not impossible) process, as we have already seen how determining whether reconsolidation is likely to occur presents challenges even in relatively simplistic settings. Continued translation of findings from experimental to clinical work and back again will therefore be required.

3.3. Translation to clinical science

Laboratory studies using experimental memory paradigms can only go so far in assessing the translational feasibility of reconsolidation-based approaches. Ultimately, concerted efforts at translation must obviously involve those suffering from genuine subclinical and clinical disorders of emotional memory, as even the most comprehensive understanding of experimentally induced memory formation and modification may stop short of elucidating how such findings can be leveraged in clinical practice.

While preliminary evidence in open-label trials revealed a reduction in trauma-related symptoms in PTSD patients (Brunet et al., 2008, 2011; Poundja et al., 2012), these initial positive effects for trauma memory could not be replicated in three follow-up randomized controlled trials testing different pharmacological agents (Wood et al., 2015). It should be noticed however that script-driven imagery was used for the reactivation of the trauma memory, whilst this method has been explicitly developed to measure retrieval of the trauma memory and *not* reconsolidation. Instead of running large-scale clinical trials to test the efficacy of a reconsolidation intervention in PTSD, we should first better understand the necessary conditions to trigger reconsolidation of trauma memory (Kindt and van Emmerik, 2016).

Research in our lab has considered whether specific phobias and subclinical fears may be an informative translational step in the development of reconsolidation-based interventions. Such fears may be quite tractable experimentally, owing to their fairly precise nature (though even specific phobias are far from simple) and the quite high frequency of such fear in the general population. Taking arachnophobia as a model, we have successfully translated the laboratory findings on conditioned fear response to a subclinical trial in individuals with spider phobia. We showed that a brief exposure ($\pm$ 2 min) to a live, large tarantula followed by 40 mg of the β-AR blocker propranolol HCl (double-blind/placebo-controlled), transformed avoidance behaviour into approach behaviour in a virtually binary fashion. These improvements in the propranolol + reactivation group, and the differences between groups (placebo, propranolol without reactivation), were not restricted to the phobic stimulus of the intervention and were maintained at a one-year follow-up, suggesting that this reconsolidation-based intervention may produce not only large but long-lasting effects. We also demonstrated that the change in fear behaviour could not be explained by a general fear-dampening effect of propranolol or by an exposure effect, because the intervention effect was only observed when the active drug propranolol was given in conjunction with memory reactivation.

Drawing from the insights on the necessary and boundary conditions for inducing memory reconsolidation in our fear-conditioning studies, we inferred that the exposure to the threat cue (i.e., spider) ought to be very brief, but the distinctive features of the retrieval session that actually trigger the process of memory reconsolidation remain elusive. We hypothesize that the actual approach behaviour towards the threat cue while feeling overwhelmed by their fear may be responsible for the process of memory reconsolidation, but this conjecture has not yet been critically tested. We have since been working with more clinical and subclinical samples of phobic participants. In a study of clinically somewhat more phobic participants than our initial study (Soeter and Kindt, 2015b), we aimed to assess the optimum means of reactivation (Elsey and Kindt, 2021). However, several difficulties may preclude a simple answer to this crucial question. Firstly, even within arachnophobia, participants' fears spanned a wide spectrum of different spider types and situations, making a controlled process difficult. In addition, owing to the difficulty of retaining participants for longer-term follow-ups and the increased difficulty of the exposure for participants, greater interaction between the therapist/experimenters and the patients was necessary than in previous studies with subclinical participants. This - in addition to the growing knowledge of the intervention -

may have led to an increase in placebo effects, which were higher in this study than in Soeter and Kindt (2015b), where they were essentially absent.

Pavlovian fear-conditioning research shows that the window to target the process of memory reconsolidation is small and relatively easy to miss: If exposure is too long to trigger reconsolidation, but too short for extinction learning, an inactive transitional limbo state occurs, rendering the fear memory unchanged and insensitive to amnesic agents (Merlo et al., 2014; Sevenster et al., 2014). Since we do not have a validated, non-invasive, independent marker that can be used during reactivation procedures to indicate whether reconsolidation is triggered or not, we have tested a behaviourally-controlled boundary condition of reconsolidation in naturalistic fears, to inform the development of future reconsolidation interventions. Specifically, in the absence of a definite prediction error event, we focussed on the duration of the reactivation procedure as an experimental proxy for the amount of prediction error. In a systematic pilot study, participants with a subclinical fear of public speaking underwent a stress inducing speech task varying in duration followed by either one pill of 40 mg propranolol or placebo. Although self-reported speech distress and public speaking anxiety showed clear reductions following treatment, the propranolol did not reliably outperform placebo, regardless of speech duration at treatment (Elsey et al., 2020). In a recent study we tested again the duration of a reactivation procedure, as an experimental proxy for the amount of PE. In this study, spider-fearful participants underwent either a brief ~3-minute or a somewhat longer ~14-minute exposure to a tarantula, intended to trigger reconsolidation or the limbo state respectively, followed by 40 mg of propranolol. We expected greater spider fear reduction after the brief than the longer exposure session. Unexpectedly, there were no group differences on any outcome measures. Both groups showed a marked reduction in fear behaviour towards a generalisation stimulus (a house spider) accompanied by lower self-reported distress, with a sharp decline in spider fear scores two days after treatment that persisted one year later (Filmer et al., 2022).

In sum, the amount of PE cannot be easily quantified in clinical practice, given that it depends entirely upon how the experience at the reactivation procedure aligns with the learning history and the strength of the memory. This makes it a huge challenge to identify absolute criteria for triggering reconsolidation in clinical practice, where the learning history and the subsequent strength of the memory are basically unknown. To facilitate effective and efficient reconsolidation interventions, we require methods to behaviourally control prediction error, regardless of learning history, that we can use to determine which process we trigger in clinical practice. This is, of course, an exceedingly difficult balancing act that we currently have little grasp of: what exactly are the relevant predictions, how much violation is too much, and when does one know when to stop? While fear conditioning may be an excellent experimental model of anxiety disorders, it remains a model, and does not give sufficient insight into the complexities of full-fledged fears and phobias. Such factors highlight that even in supposedly 'simple' anxiety disorders, complexity is an order of magnitude above that encountered in experimental studies where learning history and reactivation can be precisely controlled. Nevertheless, we have achieved striking reductions in phobic symptoms across a range of different fears in uncontrolled settings (e.g., Elsey and Kindt, 2017a; Kindt and van Emmerik, 2016). While there are many hurdles for the realisation of reconsolidation-based treatments, we believe they remain viable.

4. Summary

The (re)discovery of memory reconsolidation at the turn of this century has had a great impact on the basic science of learning and memory, and more recently on clinical science as well. The observation of pharmacologically induced post-reactivation amnesia for learned fear is well-established in the laboratory. However, the clinical translation of these observations has proven challenging, with some studies highlighting the great promise of such an approach, and others the many difficulties.

Advocates of other therapeutic approaches, which were not designed as reconsolidation interventions, have also shown a growing interest in the phenomenon of memory reconsolidation, claiming reconsolidation as a mechanism of change. The history of psychology has shown how much more difficult it is to understand why a treatment works than 'merely' to show that it does, and it is common to consider novel mechanisms as explanations for observed effects. Such speculations may be warranted, but of course vary in their rigor. Simply drawing parallels or observing similarities is surely insufficient. In particular, claims that because a treatment involves reactivating a memory, administering some kind of intervention, and then observing a change, is strongly suggestive of reconsolidation underpinning a treatment effect (Lane et al., 2015; Lane, 2018) are largely unconvincing: almost all psychotherapeutic interventions could be subsumed under such a framework. To really advance the field of reconsolidation, such claims should be made carefully, and as part of research lines aiming to really test whether observed effects are most consistent with reconsolidation, or some other process (Elsey et al., 2018). We believe the greatest advances will in any case be made if reconsolidation can be purposely harnessed in a novel intervention explicitly designed to make use of the phenomenon, rather than by explaining existing therapies as involving reconsolidation. While we are aiming to harness reconsolidation for therapeutic purposes, reconsolidation is not itself necessarily the therapeutic goal: it is a hypothesised process that one aims to manipulate in a particular way.

Over the last decade we have witnessed considerable progress in understanding the critical conditions to trigger and observe memory reconsolidation in humans. The success of the reconsolidation intervention depends on subtle differences in the reactivation procedure, and the window to actually target the process of memory reconsolidation is specific and relatively small. The induction of reconsolidation is a subtle process: prediction error appears to be required for memory labilization, but with extended reactivation and/or multiple prediction errors, the window to target the fear memory may already be missed. Understanding the critical conditions for triggering reconsolidation in clinical practice is further complicated by the absence of a single universally effective procedure to induce memory reconsolidation. Whether any given reactivation triggers memory reconsolidation depends not only on the reactivation procedure itself, but also on individual differences in learning history and temperament. Irrespective of the great advances that have been made in understanding memory reconsolidation in the laboratory, the critical parameters governing the persistent mitigation of emotional memory in clinical practice remain unknown. In our future research we aim to further unravel potential boundary and optimal conditions for targeting the process of memory reconsolidation in a range of fears and phobias. Translating research on memory reconsolidation from animal models to human fear-conditioning experiments, and perhaps even to effective reconsolidation-based therapies is an exciting prospect, with the potential to signify a paradigm shift in the treatment of emotional memory disorders.

CRediT authorship contribution statement

Merel Kindt: Conceptualization, Writing – original draft, Writing – review & editing. **James W.B. Elsey:** Writing – review & editing.

Data Availability

No data was used for the research described in the article.

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Competing Interests

Merel Kindt is the co-founder of Kindt Clinics, an outpatient clinic for fears and phobias where people are treated with the memory reconsolidation intervention.

References

Baldwin, D.S., Anderson, I.M., Nutt, D.J., Allgulander, C., Bandelow, B., den Boer, J.A., Wittchen, H.U., 2014. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for psychopharmacology. J. Psychopharmacol. 28 (5), 403–439.

Bos, M.G., Beckers, T., Kindt, M., 2012. The effects of noradrenergic blockade on extinction in humans. Biol. Psychol. 89 (3), 598–605.

Bos, M.G.N., Beckers, T., Kindt, M., 2014. Noradrenergic blockade of memory reconsolidation: a failure to reduce conditioned fear responding. Front. Behav. Neurosci. 8, 412.

Bouton, M.E., 2002. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol. Psychiatry 52 (10), 976–986.

Brunet, A., Orr, S.P., Tremblay, J., Robertson, K., Nader, K., Pitman, R.K., 2008. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. J. Psychiatr. Res. 42 (6), 503–506.

Brunet, A., Poundja, J., Tremblay, J., Bui, É., Thomas, É., Orr, S.P., Pitman, R.K., 2011. Trauma reactivation under the influence of propranolol decreases posttraumatic stress symptoms and disorder: 3 open-label trials. J. Clin. Psychopharmacol. 31 (4), 547–550.

Chalkia, A., Weermeijer, J., Van Oudenhove, L., Beckers, T., 2019. Acute but not permanent effects of propranolol on fear memory expression in humans. Front. Hum. Neurosci. 13, 51.

Cogan, E.S., Shapses, M.A., Robinson, T.E., Tronson, N.C., 2018. Disrupting reconsolidation: memory erasure or blunting of emotional/motivational value? Neuropsychopharmacology 1 (Advance online proof).

Craske, M.G., Treanor, M., Conway, C.C., Zbozinek, T., Vervliet, B., 2014. Maximizing exposure therapy: an inhibitory learning approach. Behav. Res. Ther. 58, 10–23.

Craske, M.G., Treanor, M., Zbozinek, T.D., Vervliet, B., 2022. Optimizing exposure therapy with an inhibitory retrieval approach and the OptEx Nexus. Behav. Res. Ther. 152, 104069.

Dębiec, J., Ledoux, J.E., 2004. Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. Neuroscience 129 (2), 267–272.

Dębiec, J., Doyère, V., Nader, K., LeDoux, J.E., 2006. Directly reactivated, but not indirectly reactivated, memories undergo reconsolidation in the amygdala. Proc. Natl. Acad. Sci. 103 (9), 3428–3433.

Díaz-Mataix, L., Martinez, R.C.R., Schafe, G.E., LeDoux, J.E., Doyère, V., 2013. Detection of a temporal error triggers reconsolidation of amygdala-dependent memories. Curr. Biol. 23 (6), 467–472.

Dudai, Y., 2009. Predicting not to predict too much: how the cellular machinery of memory anticipates the uncertain future. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 364 (1521), 1255–1262.

Eisenberg, M., Kobilo, T., Berman, D.E., Dudai, Y., 2003. Stability of retrieved memory: inverse correlation with trace dominance. Science 301 (5636), 1102–1104.

Elsey, J., Kindt, M., 2016. Manipulating human memory through reconsolidation: ethical implications of a new therapeutic approach. AJOB Neurosci. 7 (4), 225–236.

Elsey, J.W., Kindt, M., 2017a. Breaking boundaries: optimizing reconsolidation-based interventions for strong and old memories. Learn. Mem. 24 (9), 472–479.

Elsey, J.W., Kindt, M., 2017b. Tackling maladaptive memories through reconsolidation: from neural to clinical science. Neurobiol. Learn. Mem. 142, 108–117.

Elsey, J.W., Kindt, M., 2021. Placebo and non-specific effects in reconsolidation-based treatment for arachnophobia. Front. Psychiatry 2003.

Elsey, J.W., Van Ast, V.A., Kindt, M., 2018. Human memory reconsolidation: a guiding framework and critical review of the evidence. Psychol. Bull. 144 (*8*), *797–848*.

Elsey, J.W., Filmer, A.I., Galvin, H.R., Kurath, J.D., Vossoughi, L., Thomander, L.S., Kindt, M., 2020. Reconsolidation-based treatment for fear of public speaking: a systematic pilot study using propranolol. Transl. Psychiatry 10 (1), 1–12.

Faliagkas, L., Rao-Ruiz, P., Kindt, M., 2018. Emotional memory expression is misleading: delineating transitions between memory processes. Curr. Opin. Behav. Sci. 19, 116–122.

Farach, F.J., Pruitt, L.D., Jun, J.J., Jerud, A.B., Zoellner, L.A., Roy-Byrne, P.P., 2012. Pharmacological treatment of anxiety disorders: current treatments and future directions. J. Anxiety Disord. 26 (8), 833–843.

Filmer, A.I., Peters, J., Bridge, L.A., Visser, R.M., Kindt, M., 2022. Over the edge: extending the duration of a reconsolidation intervention for spider fear. Transl. Psychiatry 12 (1), 1–10.

Finnie, P.S., Nader, K., 2012. The role of metaplasticity mechanisms in regulating memory destabilization and reconsolidation. Neurosci. Biobehav. Rev. 36 (7), 1667–1707.

Frankland, P.W., Ding, H.K., Takahashi, E., Suzuki, A., Kida, S., Silva, A.J., 2006. Stability of recent and remote contextual fear memory. Learn. Mem. 13 (4), 451–457.

Gerlicher, A.M., Verweij, S.A., Kindt, M., 2022. Better, worse, or different than expected: on the role of value and identity prediction errors in fear memory reactivation. Sci. Rep. 12 (1), 1–12.

Gershman, S.J., Monfils, M.H., Norman, K.A., Niv, Y., 2017. The computational nature of memory modification. Elife 6, e23763.

Hofmann, S.G., Smits, J.A., 2008. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J. Clin. Psychiatry 69 (4), 621–632.

Hofmann, S.G., Asmundson, G.J., Beck, A.T., 2013. The science of cognitive therapy. Behav. Ther. 44 (2), 199–212.

Jakubovski, E., Johnson, J.A., Nasir, M., Müller-Vahl, K., Bloch, M.H., 2019. Systematic review and meta-analysis: dose–response curve of SSRIs and SNRIs in anxiety disorders. Depress Anxiety 36 (3), 198–212.

Johansen, J.P., Díaz-Mataix, L., Hamanaka, H., Ozawa, T., Ycu, E., Koivumaa, J., LeDoux, J.E., 2014. Hebbian and neuromodulatory mechanisms interact to trigger associative memory formation. Proc. Natl. Acad. Sci. 111 (51), E5584–E5592.

Kessler, R.C., Chiu, W.T., Demler, O., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 62 (6), 617–627.

Kindt, M., 2014. A behavioural neuroscience perspective on the aetiology and treatment of anxiety disorders. Behav. Res. Ther. 62, 24–36.

Kindt, M., 2018. The surprising subtleties of changing fear memory: a challenge for translational science. Philos. Trans. R. Soc. B 373 (1742), 20170033.

Kindt, M., Soeter, M., 2018. Pharmacologically induced amnesia for learned fear is time and sleep dependent. Nat. Commun. 9 (1), 1316.

Kindt, M., van Emmerik, A., 2016. New avenues for treating emotional memory disorders: towards a reconsolidation intervention for posttraumatic stress disorder. Ther. Adv. Psychopharmacol. 6 (4), 283–295.

Kindt, M., Soeter, M., Vervliet, B., 2009. Beyond extinction: erasing human fear responses and preventing the return of fear. Nat. Neurosci. 12 (3), 256–258.

Lane, R.D., 2018. From reconstruction to construction: the power of corrective emotional experiences in memory reconsolidation and enduring change. J. Am. Psychoanal. Assoc. 66 (3), 507–516.

Lane, R.D., Ryan, L., Nadel, L., Greenberg, L., 2015. Memory reconsolidation, emotional arousal, and the process of change in psychotherapy: new insights from brain science. Behav. Brain Sci. 38, *1–64*.

Lee, J.L., Milton, A.L., Everitt, B.J., 2006. Reconsolidation and extinction of conditioned fear: inhibition and potentiation. J. Neurosci. 26 (39), 10051–10056.

Lipp, O.V., Waters, A.M., Luck, C.C., Ryan, K.M., Craske, M.G., 2020. Novel approaches for strengthening human fear extinction: the roles of novelty, additional USs, and additional GSs. Behav. Res. Ther. 124, 103529.

Loerinc, A.G., Meuret, A.E., Twohig, M.P., Rosenfield, D., Bluett, E.J., Craske, M.G., 2015. Response rates for CBT for anxiety disorders: need for standardized criteria. Clin. Psychol. Rev. 42, 72–82.

Merlo, E., Milton, A.L., Goozée, Z.Y., Theobald, D.E., Everitt, B.J., 2014. Reconsolidation and extinction are dissociable and mutually exclusive processes: behavioral and molecular evidence. J. Neurosci. 34 (7), 2422–2431.

Milekic, M.H., Alberini, C.M., 2002. Temporally graded requirement for protein synthesis following memory reactivation. Neuron 36 (3), 521–525.

Morris, R.G., Inglis, J., Ainge, J.A., Olverman, H.J., Tulloch, J., Dudai, Y., Kelly, P.A., 2006. Memory reconsolidation: sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus during encoding and retrieval. Neuron 50 (3), 479–489.

Nader, K., Schafe, G.E., Le Doux, J.E., 2000. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406 (6797), 722–726.

Otis, J.M., Werner, C.T., Mueller, D., 2015. Noradrenergic regulation of fear and drug-associated memory reconsolidation. Neuropsychopharmacology 40 (4), 793–803.

Pedreira, M.E., Pérez-Cuesta, L.M., Maldonado, H., 2004. Mismatch between what is expected and what actually occurs triggers memory reconsolidation or extinction. Learn. Mem. 11 (5), 579–585.

Poundja, J., Sanche, S., Tremblay, J., Brunet, A., 2012. Trauma reactivation under the influence of propranolol: an examination of clinical predictors. Eur. J. Psychotraumatol. 3 (1), 15470.

Przybyslawski, J., Roullet, P., Sara, S.J., 1999. Attenuation of emotional and nonemotional memories after their reactivation: Role of β adrenergic receptors. J. Neurosci. 19 (15), 6623–6628.

Rescorla, R.A., Wagner, A.R., 1972. A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. Class. Cond. II: Curr. Res. Theory 2, 64–99.

Robinson, M.J.F., Franklin, K.B.J., 2010. Reconsolidation of a morphine place preference: impact of the strength and age of memory on disruption by propranolol and midazolam. Behav. Brain Res. 213 (2), 201–207.

Schroyens, N., Beckers, T., Kindt, M., 2017. In search for boundary conditions of reconsolidation: a failure of fear memory interference. Front. Behav. Neurosci. 11, 65.

Sevenster, D., Beckers, T., Kindt, M., 2012. Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. Neurobiol. Learn. Mem. 97 (3), 338–345.

Sevenster, D., Beckers, T., Kindt, M., 2013. Prediction error governs pharmacologically induced amnesia for learned fear. Science 339 (6121), 830–833.

Sevenster, D., Beckers, T., Kindt, M., 2014. Prediction error demarcates the transition from retrieval, to reconsolidation, to new learning. Learn. Mem. 21 (11), 580–584.

Soeter, M., Kindt, M., 2010. Dissociating response systems: erasing fear from memory. Neurobiol. Learn. Mem. 94 (1), 30–41.

Soeter, M., Kindt, M., 2011. Disrupting reconsolidation: pharmacological and behavioral manipulations. Learn. Mem. 18 (6), 357–366.

Soeter, M., Kindt, M., 2012a. Stimulation of the noradrenergic system during memory formation impairs extinction learning but not the disruption of reconsolidation. Neuropsychopharmacology 37 (5), 1204–1215.

Soeter, M., Kindt, M., 2012b. Erasing fear for an imagined threat event. Psychoneuroendrocrinology 37 (*11*), 1769–1779.
Soeter, M., Kindt, M., 2015a. Retrieval cues that trigger reconsolidation of associative fear memory are not necessarily an exact replica of the original learning experience. Front. Behav. Neurosci. 9, 122.
Soeter, M., Kindt, M., 2015b. An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. Biol. Psychiatry 78 (12), 880–886.
Stemerding, L.E., Stibbe, D., van Ast, V.A., Kindt, M., 2022. Demarcating the boundary conditions of memory reconsolidation: an unsuccessful replication. Sci. Rep. 12 (1), 1–13.
Suzuki, A., Josselyn, S.A., Frankland, P.W., Masushige, S., Silva, A.J., Kida, S., 2004. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J. Neurosci. 24 (20), 4787–4795.
Waelti, P., Dickinson, A., Schultz, W., 2001. Dopamine responses comply with basic assumptions of formal learning theory. Nature 412 (6842), 43–48.
Wang, S.H., de Oliveira Alvares, L., Nader, K., 2009. Cellular and systems mechanisms of memory strength as a constraint on auditory fear reconsolidation. Nat. Neurosci. 12 (7), 905–912.
Winters, B.D., Tucci, M.C., DaCosta-Furtado, M., 2009. Older and stronger object memories are selectively destabilized by reactivation in the presence of new information. Learn. Mem. 16 (9), 545–553.
Wittchen, H.U., Jacobi, F., 2005. Size and burden of mental disorders in Europe—a critical review and appraisal of 27 studies. Eur. Neuropsychopharmacol. 15 (4), 357–376.
Wood, N.E., Rosasco, M.L., Suris, A.M., Spring, J.D., Marin, M.F., Lasko, N.B., Pitman, R. K., 2015. Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: three negative psychophysiological studies. Psychiatry Res. 225 (1–2), 31–39.