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Memory Reconsolidation Interference as an Emerging Treatment for Emotional Disorders: Strengths, Limitations, Challenges and Opportunities

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Abstract

Experimental research on emotional memory reconsolidation interference, or the induction of amnesia for previously established emotional memory, has a long tradition, but the potential of that research for the development of novel interventions to treat psychological disorders has been recognized only recently. Here we provide an overview of basic research and clinical studies on emotional memory reconsolidation interference. We point out specific advantages of interventions based on memory reconsolidation interference over traditional treatment for emotional disorders. We also explain how findings from basic research suggest limitations and challenges to clinical translation that may help to understand why clinical trials have met with mixed success so far and how their success can be increased. In closing, we preview new intervention approaches beyond the induction of amnesia that the phenomenon of memory reconsolidation may afford for alleviating the burden imposed by emotional memories and comment on theoretical controversies regarding the nature of memory reconsolidation.

Keywords

Emotional memory; Amnesia; Reconsolidation; Anxiety; PTSD; Addiction

Introduction

Memories with a strong emotional connotation play a pathogenic role in a variety of emotional disorders, including anxiety disorders, post-traumatic stress disorder (PTSD), addiction, and depression (Brewin 2011; Kindt 2014; Milton & Everitt 2012; Williams et al. 2007). What if it were possible to alleviate the burden imposed by those memories by taking a pill or by another simple intervention that would somehow help us to permanently forget them or strip them of their emotional charge? The present review investigates whether this is

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a science fiction or an impending reality, and spells out the theoretical and empirical issues that need to be resolved for this question to be decided.

Remarkably perhaps, it has been known for almost 50 years that it is possible to induce selective amnesia for a previously established fear memory in the lab (*post-retrieval amnesia*; Misanin et al. 1968). Yet the clinical potential of this finding for the treatment of emotional disorders was not recognized for another 30 years (Nader et al. 2000; Przybyslawski et al. 1999), and empirical translation to humans of this kind of amnesia for emotional memory, often referred to as *memory reconsolidation interference*, did not happen until less than a decade ago (Kindt et al. 2009). We first present a concise historical overview of basic research on emotional memory reconsolidation and the ways it can supposedly be interfered with. We also briefly review findings from clinical studies that have tried to translate the principle of memory reconsolidation interference to the treatment of emotional disorders and which have yielded rather mixed results. Along the way, we point out why memory reconsolidation interference may actually be a somewhat unfortunate label for the empirical phenomenon under consideration. In the remainder of this review, we discuss the potential *advantages* over existing treatments that inducing post-retrieval amnesia offers for the treatment of emotional disorders, the *limitations* to its application, the *challenges* involved in successful clinical translation and the unique *opportunities* for future interventions that may be afforded by the phenomenon of memory reconsolidation. A recurring theme will be how further basic research and theoretical progress regarding the nature of emotional memory and its modification will inform the future of memory reconsolidation interference as an effective intervention for emotional disorders.

Emotional Memories: What We've Known about Forgetting Them

In a first section of our review, we revisit basic and clinical research on the induction of amnesia for previously established emotional memories. While much of the research that we review focuses on the modification of fear memories, we will in passing point to applications in appetitive disorders (addiction) and depression as well.

Turning back (in) time: Inducing post-retrieval amnesia for emotional memories

In 1968, Misanin and colleagues published a study that shattered the tenets of standard theories of memory consolidation. On a first day of training, they taught rats to fear an auditory cue (conditioned stimulus, CS), by pairing the presentation of that cue with the administration of a footshock (unconditioned stimulus, US) in a Pavlovian fear conditioning procedure. The animals exhibited a clear fear response to the tone CS when it was presented two days later, indicating that they had indeed acquired a memory associating the tone with footshock. In keeping with previous research, Misanin et al. (1968) also observed that such a conditioned fear response on day 3 was absent in animals that had received a strong electroconvulsive shock (ECS) shortly after the initial tone-footshock training on day 1. This was consistent with the idea that during initial consolidation, memory traces are sensitive to disruption so that an intervention like ECS that interrupts the consolidation process will yield retrospective amnesia for the events immediately preceding that intervention (Duncan 1949). More importantly, Misanin et al. went on to show that in animals where consolidation

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had been allowed to proceed without interference on day 1 and a fear memory was supposedly in place, similar amnesia could be induced by giving the animals ECS not during consolidation on the initial training day but on day 2, right after they were presented with a reminder for the fear memory acquired on day 1 (i.e., a presentation of the auditory CS, without the US). So, if these animals were tested on day 3, they showed no indication of having a fear memory involving the auditory cue, just like the animals that had received ECS right after the initial CS-US training. This observation squarely contradicted the idea that memories are impervious to disruption after consolidation has completed and represented the first demonstration of experimentally induced amnesia for a previously established, reactivated fear memory.

The findings of Misanin and colleagues had a huge impact and spawned a lot of debate and follow up research. However, they were regarded exclusively in light of their implications for the standard theory of memory consolidation, not as a potential treatment to get rid of unwanted or debilitating emotional memories (for an obscure exception, see Rubin 1976). Part of the reason may have been that in early studies post-retrieval induced amnesia often turned out to be less robust and long-lasting than amnesia induced immediately upon learning (e.g., DeVietti & Larson 1971; Judge & Quartermain 1982; Mactutus et al. 1979) and that post-retrieval amnesia sometimes appeared to be reversible (e.g., Bregman et al. 1976; although the same had occasionally been found for immediate amnesia as well, e.g., Quartermain et al. 1972).

Reconciliation between the basic notions of consolidation theory and the observation that it is possible to interfere with a memory long after its alleged consolidated period has passed, emerged from the proposal that memory retrieval can lead to the *destabilization* of a consolidated memory trace, inducing the need for a time-limited process of protein-synthesis dependent *reconsolidation* (Przybyslawski & Sara 1997; Sara 2000). During reconsolidation, it was proposed, many of the same neurobiological processes that initially take place during consolidation are repeated. According to this idea, at any moment, a memory can be in one of two states, an active, unstable state (in the minutes to hours after it has been acquired or reactivated by retrieval) or an inactive, stable state (after consolidation and in the absence of reactivation). In the active state, the memory trace requires DNA transcription and protein synthesis to be (re)stabilized into an inactive state. The active state thus offers a window of opportunity to interfere with the integrity of the memory trace, through the disruption of those neurobiological processes.

Evidence for the reconsolidation hypothesis came from studies showing that pharmacological blockade of protein synthesis processes that had been demonstrated to be critical for fear memory consolidation, through infusion in the amygdala of a protein synthesis inhibitor like anisomycin (Nader et al. 2000) or administration of an NMDA-receptor antagonist like AP5 after retrieval of conditioned fear memory (Summers et al. 1997), prevented expression of that memory the next day. These findings suggested that it is not the newness of a memory per se, but whether the memory is in an active, unstable state, which determines its susceptibility to amnestic treatments that interfere with (re)consolidation (Sara 2000).

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Of particular importance was the observation that the post-retrieval amnesia for emotional memory that was obtained using those pharmacological agents was typically robust and long-lasting. In rats, complete amnesia could be observed up to several weeks following infusion of the β-adrenergic receptor antagonist propranolol in the amygdala after reactivation of a conditioned fear memory (Debiec & LeDoux 2004) – if reconsolidation interference was ever going to result in a feasible intervention to reduce the burden imposed by emotional memories in PTSD and other emotional disorders, it's effects had to be more than transient.

An initial hurdle in the translation and application to humans of findings regarding reconsolidation interference in animals was the nature of the interventions that were used to disrupt reconsolidation. Initial animal studies had relied mostly on ECS to induce amnesia after memory reactivation. While sometimes used as a last-resort treatment for refractory depression in humans (Kellner et al. 2012), an intervention that involves eliciting epileptic insults and that is characterized by considerable cognitive side-effects does not strike as a particularly attractive novel intervention for the large-scale treatment of emotional disorders. The bulk of later studies in animals had blocked protein synthesis during reconsolidation using pharmacological agents with considerable toxicity (e.g., anisomycin, which completely blocks protein synthesis; Judge & Quartermain 1982; Nader et al. 2000) or had induced amnesia through NMDA receptor blockade after memory reactivation by administering compounds with serious adverse side effects (e.g., MK-801, which is neurotoxic and causes psychotic symptoms; Przybyslawski & Sara 1997). Other studies had induced post-retrieval amnesia by immersing animals in cold water to produce severe hypothermia (Mactutus et al. 1979). None of those interventions seemed readily translatable to humans. Around the turn of the century, however, it was found that amnesia for conditioned fear memories could also be induced in rats through administration of propranolol after memory reactivation (Debiec & LeDoux 2004; Przybyslawski et al. 1999). Propranolol acts by blocking β-adrenergic receptors; β-adrenergic receptors play an essential role in protein synthesis necessary for synaptic plasticity via the downstream cAMP-PKA-CREB signaling pathway (Otis et al. 2015). Of prime importance, at the body-weight adjusted doses used for inducing experimental amnesia in rodents, propranolol is perfectly safe for use in healthy humans; in fact, similar doses are taken on a daily basis by millions of people worldwide as a treatment for hypertension. The observation of amnesia through administration of propranolol after memory reactivation therefore opened major perspectives for clinical translation.

A major milestone in the process of clinical translation was the first demonstration of the amnestic effect of propranolol on a reactivated fear memory in humans (Kindt et al. 2009). In our study, human volunteers received differential Pavlovian fear conditioning on day 1 – CS_A was repeatedly paired with a mild shock, whereas CS_B was not followed by shock. On day 2, participants received propranolol or placebo (double-blind) before being presented with CS_A once, without shock, to reactivate the fear memory established on day 1. When tested for differential fear responding on day 3, participants that had received propranolol before memory reactivation exhibited a complete lack of differential fear responding, unlike participants that had received placebo or participants that had received propranolol without memory reactivation. More precisely, participants exhibited a complete lack of differential

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fear-potentiated startle (FPS) responding to CS_A and CS_B. The startle response is an amygdala-initiated fear response that is considered to reflect the activation of the brain's subcortical defense system (LeDoux 2003; Walker & Davis 2002). Responding to a startle probe such as a sudden noise burst is typically enhanced during negative emotional states such as the fear elicited by a CS that has been paired with an aversive US (Lang et al. 2000); the lack of enhanced responding to CS_A on day 3 therefore indicates amnesia for the conditioned fear memory acquired on day 1. Of note, administration of propranolol upon reactivation did not induce amnesia at a declarative level: Participants exhibited intact knowledge of the CS-US contingencies, and in later studies also intact differential skin conductance responding to the CSs (e.g., Soeter & Kindt 2010), on day 3 – skin conductance responding has been argued to rely on more cortical (fear) learning circuits and tends to closely track contingency knowledge in fear conditioning, unlike FPS (Sevenster et al. 2014a; Weike et al. 2005). The finding that propranolol blocks fear memory retrieval at a non-declarative level but leaves intact the declarative memory for the event that gave rise to it, helps to assuage ethical concerns about the pharmacological induction of amnesia for past fearful events (Otis et al. 2015; see box HOW DESIRABLE IS THE SPOTLESS MIND?). Our findings indeed suggest that the intervention is not in fact making one forget what happened, it rather seems to make one less emotionally affected by remembering what happened, as if the emotional edge were removed from the memory. Corroborating evidence that propranolol administration upon memory retrieval induces amnesia for the emotional aspect of a fear memory without affecting declarative memory for the same event has meanwhile also been obtained in mice (Villain et al. 2016).

Many ways to forget your fears

In concert with seminal efforts to demonstrate pharmacologically induced post-retrieval amnesia for emotional memory in humans, researchers started to investigate alternative approaches for leveraging the phenomenon of memory reconsolidation to attenuate emotional memories. One intriguing step in this direction was the demonstration, in animals as well as in humans, of a phenomenon called *behavioral memory updating* (Monfils et al. 2009; Schiller et al. 2010). Like in studies of pharmacologically-induced post-retrieval amnesia, a conditioned fear memory is first installed through Pavlovian fear conditioning and then reactivated the next day by presenting the conditioned fear CS once, without reinforcement. Next, however, rather than an amnestic drug that impairs reconsolidation, corrective information is presented, aimed at modifying the reactivated memory trace. In particular, after a brief delay, humans or animals are repeatedly presented with the fear CS, without reinforcement. This procedure of repeated presentation of a previously established CS is called extinction training. It normally results in the gradual reduction of conditioned fear responding elicited by the CS, reflecting the formation of an extinction memory trace that competes with the original fear memory for retrieval (Bouton 2004; Hermans et al. 2006). A major limitation of regular extinction training is that the reduction in conditioned responding that it achieves is not permanent: Several factors can cause the original fear memory to dominate over the extinction memory and control behavior again, including a change of context after extinction training (in which case the return of fear is called *renewal*), the presentation of one or more unsignaled USs (*reinstatement*), or the mere passage of time (*spontaneous recovery*). Extinction training is regarded as a partial

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laboratory model for exposure treatment, in which a patient with an anxiety disorder is repeatedly exposed to cues or situations that elicit fear in order to gradually reduce the fear for those signals (Bouton et al. 2001). It has been argued that the recovery-from-extinction phenomena that occur when fear memory comes to dominate over extinction memory again may play a critical role in the lack of endurance of the clinical improvement that is sometimes observed from exposure treatment (Bouton 1988). Even though exposure is the most effective treatment currently available for a number of emotional memory disorders, relapse indeed remains a major challenge (Vervliet et al. 2013)

In the experiments of Monfils et al. (2009) in rats and Schiller et al. (2010) in humans, however, effects of extinction training, when timed to overlap with the time window of fear memory reconsolidation induced by the reactivation trial, appeared to be insensitive to recovery manipulations and long-lasting (complete elimination of conditioned fear responding and resistance to reinstatement was observed up to one year later in humans). This was not the case when extinction was performed without prior memory reactivation or when extinction training was delayed until after the reconsolidation of the reactivated fear memory was completed; under those latter conditions, extinction was equally effective on the short term, but conditioned responding did show sensitivity to reinstatement and spontaneous recovery. The permanent fear reduction that was achieved when extinction training was conducted within the reconsolidation window was cause for the authors to argue that extinction training in that case did not result in the formation of a separate, competitive extinction memory trace but served to permanently modify the initial fear memory itself, rendered active through reactivation. This interpretation fits with the notion that the functional role of reconsolidation is to allow for memories to be updated in the face of corrective information (Lee 2009; see below): Memory reactivation prior to extinction training renders the initial fear memory malleable, so that the corrective information supplied by the extinction training leads to a modification of that memory, rather than to the formation of a separate extinction memory.

Promising as those findings might be, it deserves mention that the behavioral memory updating effect has not been widely replicated thus far (unlike pharmacologically-induced post-retrieval amnesia, which has been demonstrated in a variety of species and using a wide range of amnestic agents). While a number of positive demonstrations have been reported in humans (see Agren et al. 2012; Oyarzún et al. 2012; Schiller et al. 2010; Steinfurth et al. 2014) as well as in animals (Clem & Huganir, 2010; Flavell et al. 2011; Monfils et al. 2009; Piñeyro et al. 2013; Rao-Ruiz et al. 2011), some studies have failed to find beneficial effects of memory reactivation prior to extinction training or have even found adverse effects (including, in humans: Golkar et al. 2012; Kindt & Soeter 2013; Meir Drexler et al. 2014; Soeter & Kindt 2011; in animals: Chan et al. 2010; Costanzi et al. 2011; Flavell et al. 2011; Ishii et al. 2012, 2015; Stafford et al. 2013; for a review of mixed findings regarding drug-related memories, see Hutton-Bedbrook & McNally 2013). As a result, some have argued that there are important boundary conditions on the phenomenon of behavioral memory updating that are yet to be uncovered (Auber et al. 2013; Kredlow et al. 2016; Schiller & Phelps 2011;). Remarkably, Baker et al. (2013) have demonstrated that a retrieval trial that is presented shortly after rather than shortly before extinction training similarly reduces the subsequent expression of conditioned fear. This suggests that the mechanism of action of

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behavioral memory updating may not in fact involve reconsolidation of the previously acquired memory trace at all, but reflect extinction memory enhancement. Clearly, more work will be needed before the technique is ready for translation to clinical interventions. On the positive side, if memory reactivation prior to extinction training can indeed be demonstrated to reliably reduce the return of fear observed after regular extinction training, a relatively minor modification to existing protocols for exposure treatment may yield considerable clinical progress in reducing relapse rates after treatment.

While rather more challenging, some efforts have also been done to demonstrate post-retrieval amnesia for specific memories in humans caused by ECS. Kroes et al. (2014) presented patients with unipolar depression, who had been referred to ECS treatment on clinical indication, with two different emotionally aversive stories that each accompanied a series of visual slides. A week later, the memory for one of the stories was reactivated by presenting the first slide from that story, shortly before the patients received their scheduled ECS treatment. When given a multiple choice test about both stories one day later, participants performed markedly worse for the story that had been reactivated before ECS treatment than for the other story; this effect did not occur in a control group that did not receive ECS after memory reactivation. These results provide a strong proof of principle for the possibility to induce amnesia in humans for previously established memories using ECS, although the interpretation of the findings is somewhat obscured by (a) the fact that ECS is known to result in marked general cognitive side-effects and (b) the fact that unlike in animals, ECT in humans is performed under general anesthesia, which makes it hard to rule out that the amnesia is caused by the anesthetic agents rather than the ECS proper. Of note, even if the effects of ECS on emotional memory reconsolidation can be corroborated and extended to self-relevant emotional memories, the intricacies of ECS administration and its considerable side-effects make it unsuitable as a candidate for wide-scale application in the treatment of emotional memory disorders.

Finally, James et al. (2015) recently demonstrated that memory intrusions for emotional events can be reduced by engaging visuospatial working memory resources after reactivation of the memory for those events. James et al. first made participants view a film clip depicting various traumatic events. The next day, some participants were presented with stills from the clip, to reactivate the trauma memory created the previous day. Ten minutes later, i.e., during the reconsolidation period, they were asked to play Tetris, a computer game that strongly engages visuospatial working memory. As a result, participants reported markedly fewer spontaneous intrusions from the trauma film over the course of the next 7 days and also exhibited less intrusions in an intrusion provocation task after a week than participants who had not played Tetris after the memory reactivation or had not received memory reactivation before getting to play Tetris on day 2. James et al. (2015) suggested that the strong engagement of visuospatial working memories after the reactivation of the trauma memory (which was highly visual in nature) presumably interfered with the reconsolidation of the unstable trauma memory, on the assumption that successful reconsolidation of a destabilized visual episodic memory implicates visual imagery processes that recruit visual working memory. Again, these findings bear great potential in principle; they might also help explain the efficacy of EMDR, a trauma intervention in which patients are asked to retrieve trauma memories while performing rhythmic left-right

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eye movements. Some have argued that the efficacy of EMDR is related to the fact that the eye movements that patients are asked to make, tax (visual) working memory (van den Hout et al 2014). So far, however, game play induced retrospective amnesia for a previously acquired analogue trauma has been reported in one paper only (James et al. 2015). Building on the same logic, we have recently begun trying to induce amnesia for previously acquired conditioned fear memories by having participants engage in a task that supposedly interferes with emotional working memory (King & Schaefer 2011) after fear memory reactivation. So far, however, we have not been able to demonstrate any beneficial effects of that intervention on the later expression of conditioned fear (Chalkia et al. 2016). More work will be needed to pinpoint whether and under what circumstances interventions that target working memory resources after emotional memory reactivation may indeed serve to induce amnesia for such memories and whether the mechanisms underlying such an effect are similar as for other forms of post-retrieval amnesia.

Reconsolidation interference: Erasing emotional memories or burying them deep?

One long-standing controversy in the field of reconsolidation interference concerns the mechanisms that govern post-retrieval amnesia. The standard view has it that memory retrieval induces destabilization of the consolidated memory trace, provoking a need for protein-synthesis dependent reconsolidation (Nader & Hardt 2009). If the reconsolidation process is disrupted, be it by ECS, amnestic drugs or other means, the memory trace is lost and amnesia occurs – (part of) the memory trace is quite literally erased. Recent findings, however, have challenged that view, demonstrating that memory can survive apparent amnesia and recover. Gisquet-Verrier et al. (2015) revealed that the suppression of fear responding, caused by administration of the protein synthesis inhibitor cycloheximide upon memory reactivation, can be reversed by re-administering cycloheximide before a later memory test. Moreover, a similar reversible amnesia can be achieved using lithiumchloride after memory reactivation and before the later memory test, despite the fact that lithiumchloride has no effect on protein synthesis and is itself a potent US for aversive learning. Those results suggest that the amnesia induced by the administration of a putative protein synthesis inhibitor or other amnestic agents need not reflect erasure of the memory trace (see also Ryan et al. 2015). Instead, the authors argue, as a result of the memory being brought back in an active state, the internal state provoked by drug administration at the time of memory retrieval will become integrated into the memory representation. This in turn renders later expression of the memory state-dependent, so that in the absence of the internal drug state amnesia occurs; this amnesia is lifted when the drug state is recreated by re-administration.

It is clear that the observations of Gisquet-Verrier et al. (2015) and Ryan et al. (2015), along with earlier observations (Riccio et al. 2006), pose a challenge for the reconsolidation hypothesis. At the same time, it is far from obvious that the state-dependent retrieval hypothesis that is proposed as an alternative provides a comprehensive account for all observations of post-retrieval amnesia. For one thing, the state-dependent retrieval account is predicated on the notion that amnestic drugs (or other amnestic treatments applied while memory is in an active state) induce a sufficiently salient internal state. While this is obvious for manipulations like the administration of potent protein synthesis inhibitors (which can

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produce considerable malaise) or the application of ECS, the elicitation of a discernable drug state is far less obvious when propranolol is used to induce post-retrieval amnesia. At the typical dose used in experimental studies and in many clinical trials, propranolol does not provoke strong subjective effects; in fact, in double-blind studies performed in our lab, if participants are asked whether they believe to have been given propranolol or placebo, the rate of participants who indicate having received propranolol is similar in the propranolol and placebo conditions. Conversely, a second problem for the state-dependent retrieval account is that, whereas administration of some drugs at the time of memory retrieval indeed produces amnesia at a later drug-free memory test, other pharmacological and non-pharmacological manipulations that are administered after memory reactivation and induce a clear internal state enhance rather than reduce memory performance on a subsequent drug-free test (e.g., Bos et al. 2014b; Gazarini et al. 2013).

All in all, it is fair to say that the exact mechanism underlying experimentally induced post-retrieval amnesia is not fully understood. At present, it seems a distinct possibility that several different mechanisms can produce amnesia. Some of those may involve genuine undoing of part of the memory trace, whereas others may rather make memory expression state-dependent. However, given the uncertainty regarding the underlying mechanism, the labeling of post-retrieval amnesia as *reconsolidation interference* is probably a bit unfortunate, because it suggests commitment to a particular type of underlying mechanism for the amnesia that is observed. *Induced post-retrieval amnesia* is a more neutral but also more cumbersome and less widely accepted description. For now, we will use both descriptors interchangeably, in a non-committal way. In the final section of the paper, we will return to the clinical implications of the controversy regarding the nature of reconsolidation interference.

From the Lab to the Clinic: Leveraging Reconsolidation Interference for the Treatment of Emotional Disorders

In particular the demonstration that post-retrieval amnesia for learned fear could be induced in the lab using a widely-prescribed and non-toxic compound like propranolol, not only in animals (Debiec & LeDoux 2004; Przybyslawski et al. 1999) but also in humans (Kindt et al. 2009), has created great impetus for more clinically oriented research in recent years, initially targeting mostly PTSD. In a small, seminal study by Brunet et al. (2008), people suffering from PTSD were asked to retrieve memories of the trauma they had endured, as input for scripts to later be used in imagery-based exposure. Some of the patients received a single dose of propranolol after the retrieval session, whereas others were given placebo, double-blind. During the later script-driven imagery, the patients given propranolol after reactivation exhibited markedly lower levels of fear reactivity (as measured through heart rate and skin conductance) than the patients given placebo. This clearly suggests that the emotional aspects of the trauma memory were remembered less readily or less strongly in the propranolol group than in the placebo group. A few open-label, non-controlled follow-up trials by the same group seemed to corroborate those observations (Brunet et al. 2011; Poundja et al. 2012). Since then, a number of studies have sought to evaluate the effects of

pharmacological reconsolidation interference in the treatment of phobia, PTSD, addiction and beyond. We review those studies below.

Unique strengths of reconsolidation interference over other approaches for reducing emotional memories

The great attraction of reconsolidation interference for the clinical treatment of emotional disorders arguably has to do with a number of specific, principled *advantages* of the approach over standard interventions for the treatment of emotional disorders. One eminent advantage that the approach seems to promise concerns the durability of its effects. As indicated above, extinction training can be just as effective as reconsolidation interference in establishing a reduction of fear responding to previously established conditioned fear cues; however, the amnesia induced by extinction training is typically not permanent (Vervliet et al. 2013). Due to the fact that the initial fear memory is unaffected, conditioned fear can eventually return (see the phenomena of *renewal*, *reinstatement* and *spontaneous recovery* described above) or be reacquired quickly (*rapid re-acquisition*). This does not bode well for the long-term efficacy of treatments like exposure treatment that rely in part on extinction training as their core ingredient; even if people gradually learn to no longer fear stimuli, situations or places that they once were afraid of, the fact that their original fear memory is intact renders the resurfacing of their fear at any moment in the future a perpetual possibility (Brown & Barlow 1995; Foa & McClean 2016). This holds also for other disorders in which cue-elicited emotional memories play a central role, such as additive disorders, where confrontation with cues associated with substance use can trigger conditioned craving that promotes drug seeking and consumption (Van Gucht et al. 2008). Here also, exposure treatment can help to reduce cue-elicited craving temporarily but may not provide a lasting elimination of the underlying memory structures.

In that light, the appeal of reconsolidation interference as an alternative intervention is obvious. A number of studies have demonstrated that the amnesia produced by pharmacological interventions that target the reconsolidation of destabilized emotional memories is robust and long-lasting, if not permanent. In our own work, we have repeatedly documented that the amnesia induced by propranolol administration following reactivation of conditioned fear memories in humans is not reversible by a reinstatement procedure: Unsignaled USs presented after the induction of the amnesia do not elicit a return of conditioned fear (Kindt et al. 2009; Soeter & Kindt 2010, 2011, 2012b, 2015b; Sevenster et al. 2012, 2013, 2014b). Equally absent are spontaneous recovery, even when tested 28 days after the induction of amnesia (Soeter & Kindt 2010), and contextual renewal (Soeter & Kindt 2012a). Finally, also reacquisition after pharmacologically induced amnesia is less rapid than after extinction training (Soeter & Kindt, 2011). Similar observations of a lack of recovery after pharmacologically induced post-retrieval amnesia have been done repeatedly in animals (e.g., Alfei et al. 2015; Debiec & LeDoux 2004). Likewise, performing extinction training during fear memory reconsolidation has been shown to induce amnesia for conditioned fear that is insensitive to spontaneous recovery and reinstatement even after a year (Schiller et al. 2009; see above). In line with those observations, in a non-blinded follow-up study to their earlier report, Brunet et al. (2014) observed that the effects of

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propranolol administration were retained in full at 4-month follow up in a sample of 22 PTSD patients.

Another unique advantage over the current treatment of first choice for many anxiety disorders, exposure, is that reconsolidation interference does not require that a patient be confronted with a feared situation time and again, until the fear gradually wanes. At least in the lab, a single reactivation session, followed by the administration of an amnestic agent or by another intervention that modifies the unstable emotional memory trace, appears to suffice for a maximal effect. This is of great value, if only because the repeated confrontation with a feared or traumatic situation implies the induction of considerable distress and anticipatory anxiety in the patient, which may be a cause for dropout in exposure treatment (Foa & McClean 2016; Markowitz et al. 2015).

It is therefore no wonder that in the wake of the report of Brunet et al. (2008), several other studies have followed that have tried to exploit reconsolidation interference for the treatment of clinically severe anxiety and addictive disorders; more recently, it has been suggested that the technique might also be of value for the treatment of depression, by reducing the emotional load of autobiographical memories that are believed to play a critical role in the etiology and maintenance of depression (Köhler et al. 2015). A few studies have yielded clear successes. For instance, we have shown that in individuals with spider phobia, a single dose of propranolol administered right after a brief (2-min) exposure to a tarantula, completely abolished patients' avoidance behavior when confronted with a spider 4 and 11 days later (Soeter & Kindt 2015a); this effect was fully preserved at 3-month and 12-month follow-up, and absent in patients given placebo (double-blind) after the brief exposure or patients given propranolol without prior exposure. In a small study in patients with substance dependence (Lonergan et al. 2016), repeated propranolol administration before the confrontation with a substance-use script gradually reduced self-reported craving elicited by the script. Such a reduction was not observed in a placebo group, but it is unclear whether the gradual decline in the propranolol group actually indicates reconsolidation interference.

Unfortunately, many other studies have failed to demonstrate beneficial effects of propranolol administration in clinical groups. In a highly-powered, randomized double-blind placebo-controlled study in smokers, Pachas et al. (2015) did not observe any effect of a single dose of propranolol administered prior to the self-generation of and subsequent confrontation with verbal smoking cues on physiological reactivity and craving during script-based imagery with the same cues one week later. In people with cocaine dependence, propranolol administered immediately after a brief cue exposure session aimed at reactivation of memories for associations between cues and cocaine administration reduced cue-elicited craving and cardiovascular reactivity one day later, but this effect was not preserved one week later and therefore does not reflect lasting amnesia (Saladin et al. 2013). Finally, a recent report of three large placebo-controlled studies in individuals with PTSD failed to find any evidence for a reduction in PTSD symptoms or physiological reactivity during exposure to trauma-related cues as a result of the administration of propranolol or the glucocorticoid (GR) antagonist mifepristone (Wood et al. 2015).

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Autobiographical memories for past life events are assumed to play a critical role in the etiology and maintenance of depression (Gotlib & Joormann 2010; Williams et al. 2007). Trials targeting the reconsolidation of such memories in people suffering from depression are lacking at present. However, evidence in healthy individuals suggests that if the retrieval of autobiographical memories is followed by exposure to a stressor (a socially evaluated cold pressor task), amnesia can afterwards be observed, but only for memories involving neutral autobiographical memories, not for memories pertaining to positive or negative events (Schwabe & Wolf 2010; see also Schwabe & Wolf 2009) – unfortunately, it is emotional autobiographical events that are the cause of suffering in depression, not neutral ones.

All in all, the clinical trials that have been performed thus far are disappointing and paint a rather mixed picture. A number of small, non-controlled studies have yielded promising results, as have a few well-controlled double-blind studies. Other studies have failed to replicate initial successes in fully randomized clinical trials. It is presently unclear what the cause is for those discrepant results; we propose that the reason may relate to intrinsic limitations to the phenomenon of memory reconsolidation interference, derived from basic research, that have not been taken into account in the majority of clinical studies. We discuss those in the following section.

Limitations to the clinical translation of reconsolidation interference: We have to learn to forget

So far, we have suggested that the retrieval of an emotional memory will destabilize the consolidated memory trace and induce a need for reconsolidation. However, it does not seem very adaptive that each time we remember something, each time we bring an event from our past back to mind, our memory for that event would become labile and sensitive to disruption. It has been proposed that the role of memory reconsolidation is to maintain memory relevance, by allowing for the integration of new information in a previously established memory trace (Lee 2009; Sara 2000; for a review, see Exton-McGuinness et al. 2015). We have previously argued that to fulfill that adaptive function, memory destabilization should occur only when at the time of retrieval, information is presented that suggests that the memory being retrieved is not entirely accurate. When at the time of retrieval no information is present that deviates from the memory being retrieved, there would be no need for memory updating. Under those circumstances, memory destabilization would cause an unnecessary need for reconsolidation and yield a risk for memory interference without conferring any benefits. It is only when at the time of memory retrieval, some sort of expectancy violation occurs that somewhat contradicts the memory, that the induction of memory destabilization and the process of reconsolidation that it necessitates would serve an adaptive function. A number of recent studies corroborate this idea. In one study from our lab, participants received differential fear conditioning on day 1 and memory reactivation followed by propranolol administration on day 2 (Sevenster et al. 2012). As in previous studies, reactivation implied a single unreinforced presentation of the CS that had been paired with a shock US on day 1. Critically, for half of the participants, shock electrodes were attached during memory reactivation; for the other half of participants, shock electrodes were not attached. As a result, the absence of shock after the CS

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presentation on day 2 carried information that was relevant to the memory established on day 1 for the former participants, but not for the latter: In the former group, a shock that was to be expected on the basis of the previously acquired memory did not occur, which should call for a slight modification of the memory and should therefore induce memory destabilization. In the latter group, administration of a shock following presentation of the CS was not to be expected, given the disconnected shock electrodes. Therefore, the absence of the US was entirely unsurprising and memory destabilization should not occur. In line with those predictions, propranolol induced amnesia in the group of participants where shock electrodes were attached on day 2, but not in the participants where electrodes were not connected. In subsequent studies, we demonstrated that memory destabilization can be triggered be a reinforced CS presentation or an unreinforced CS presentation alike, if reinforcement had been unpredictable on day 1 (i.e., reinforcement was given on half of the fear learning trials); however, if reinforcement had been entirely predictable on day 1, a reinforced reactivation trial on day 2 failed to make the fear memory sensitive to propranolol-induced amnesia (Sevenster et al. 2013). Similar observations have been done in rats: When a mismatch occurs between the presentation or the timing of the US during memory retrieval and initial training, sensitivity to drug-induced amnesia occurs; when the parameters of training and retrieval are identical, no sensitivity of the memory to the effects of amnestic drugs is observed (Alfei et al. 2015; Diaz-Mataix et al. 2013; Morris et al. 2006; Pedreira et al. 2004).

The notion that memory destabilization will occur only when there is an expectancy violation at the time of memory retrieval, or a mismatch between the retrieved memory and the actual events at that time, puts an important constraint on the possibility to interfere with emotional memory. It is fair to say that that constraint has not been taken into account in the majority of clinical trials that have been conducted so far. For instance, in the PTSD trials, script-driven imagery was used for the reactivation of the trauma memory; this method has been explicitly developed to induce strong retrieval of the trauma memory but not expectancy violation, and is therefore unlikely to induce destabilization of the trauma memory (Kindt & van Emmerik 2016). So far, no studies have systematically manipulated the presence of surprise or expectancy violation during memory retrieval in clinical trials, so our proposal that this factor may help explain the lack of consistent results in clinical trials of reconsolidation interference must remain speculative for now.

A further complication that emerges from basic research on memory reconsolidation is that the optimal degree of expectancy violation or *prediction error* during memory retrieval to induce memory destabilization may be fairly narrow. As we argued above, a lack of prediction error during retrieval will basically leave the memory trace in an inactive state. A limited degree of mismatch between the memory and events at the time of retrieval will induce memory destabilization. However, if the events at the time of memory retrieval are too discrepant to be reconciled with the initial memory trace, the formation of a novel memory trace will be initiated rather than the destabilization of the retrieved memory trace. One example is when repeated unreinforced CSs are presented during memory reactivation, like in extinction training. Rather than destabilizing a previously acquired fear memory, such extinction training will lead to the formation of an extinction memory trace. Propranolol administration may then interfere with the consolidation of the extinction memory rather

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than impairing reconsolidation of the inactive fear memory (Bos et al. 2012). The transition from insufficient prediction error to sufficient prediction error to excessive prediction error for inducing memory destabilization may be quite subtle, as illustrated by a recent study from our lab. In that study, participants were fear conditioned on day 1 using a 50% reinforcement schedule, in such a way that they could expect the CS to be followed by shock every other trial. During memory reactivation on day 2, participants received either one, two, or four unreinforced presentations of the CS, followed by the administration of propranolol. On day 3, when the CS was again presented, amnesia for the fear memory acquired on day 1 was obtained in the group of participants that had received two unreinforced CS presentations on day 2 only (Sevenster et al. 2014b). A single unreinforced presentation on day 2 did not instantiate any prediction error, given the partial reinforcement schedule in place on day 1; therefore, memory destabilization should not have occurred in that group. Two consecutive unreinforced CS presentations did violate the reinforcement pattern established on day 1; apparently, the resulting prediction error was sufficient to make the fear memory sensitive to pharmacological disruption. Four unreinforced CS presentations on day 2 presented a more extensive violation of the expected reinforcement pattern; this degree of expectancy violation turned out to be too much already to induce memory destabilization. Similar findings have recently been reported in a contextual fear conditioning procedure in rats (Alfei et al. 2015): Here, a small degree of temporal expectancy violation during memory retrieval conferred sensitivity to experimental amnesia, whereas a moderate degree of expectancy violation during retrieval rendered the subsequent administration of an amnestic drug without effect. Of importance, an even larger degree of expectancy violation during retrieval resulted in the amnestic drug preventing rather than facilitating fear reduction, in line with the idea that the drug acted to disrupt the consolidation of an extinction memory trace rather than the reconsolidation of the initial fear memory trace under those circumstances (see also Merlo et al. 2014).

The observation that there is only a narrow degree of expectancy violation that allows for the induction of amnesia upon memory retrieval obviously represents a major limitation for the translation into effective clinical interventions. It remains to be seen whether it will be feasible to establish in a principled way for how to elicit an optimal level of expectancy violation during memory retrieval in the individualized context of clinical treatment. It may be particularly challenging to achieve destabilization of relevant memories if disorders are characterized not by the anticipated repetition of a remembered event (like in panic disorder or drug-use related memories) but by intrusive memories of a trauma where memory retrieval is not accompanied by the expectation of the actual traumatic event repeating itself – such memories may not be violated as easily, because they do not imply an expectation of the traumatic event happening. Here, a fruitful approach may be to challenge patients' expectations or predictions regarding the negative consequences of actually reactivating their most painful trauma memories (like the fear that they might lose control and go crazy or that they might get completely overwhelmed; Kindt & van Emmerik 2016). Still, it remains to be determined whether that will produce destabilization of the actual trauma memories rather than the accompanying cognitions. More basic and translational research will be indispensable if we are to reach a better, more refined understanding of the critical processes that govern reactivation and destabilization of clinically relevant emotional memories.

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Further challenges for the translation of reconsolidation interference to clinical interventions

The need for an optimal degree of expectancy violation or prediction error during memory retrieval in order to induce memory destabilization puts a clear constraint on the application of reconsolidation interference in clinical practice. But other characteristics of the memory reactivation experience may represent a challenge for the induction of memory destabilization as well. One example with great clinical relevance is the use of so-called *generalization stimuli* for memory retrieval. After a fear learning episode, fear will be elicited not only by the cues that were actually involved in fear learning but also by cues that perceptually or conceptually resemble those cues. So, in a Pavlovian fear conditioning procedure, after the repeated pairing of a CS with the US, presentation of the CS will elicit a conditioned fear response, as will the presentation of any cue that sufficiently resembles the CS. In many cases, responding elicited by a generalization stimulus (GS) can be as strong as the response elicited by the CS. As a simple example, after you get robbed in a dark alley by a dark-haired man in a raincoat, you might feel the shivers run over your back not only when you meet this particular person again, but anytime you spot a dark-haired guy or a man wearing a long coat. Generalization processes like these are a key factor in the development of anxiety disorders – more than Pavlovian fear learning itself, which is largely adaptive, excessive generalization is what causes of a proliferation of anxiety to situations and cues that are not actually dangerous (Beckers et al. 2013; Dymond et al. 2015; Kindt 2014).

Clinically, the phenomenon of generalization represents a considerable challenge for treatment. In exposure therapy, stimuli and situations to be included in treatment are typically selected on the basis of the fact that they elicit a considerable amount of fear – in terms of our example above, a patient would be confronted with dark-haired men in raincoats. However, basic research suggests that such an intervention may have a limited efficacy if it does not include exposure to the original cue to which fear was initially established: Research in humans and in rodents indicates that extinction training using a GS, even if that GS elicits as much fear as the original CS, will not at all diminish the fear response to that CS; conversely, extinction training using the CS does eliminate fear responding to the GS (Boddez et al. 2012; Vervliet et al. 2005). This suggests that there is an asymmetry in generalization between a CS and a GS: Whereas extinction training for a CS reduces fear to the CS as well as a GS, extinction training for a GS reduces fear for the GS but leaves fear for the CS intact (thereby presumably preserving generalized fear responding to other GSs as well).

Given the above, it is at present unclear whether the presentation of a generalization stimulus for memory retrieval, rather than a cue actually involved in the original fear learning episode, can successfully induce destabilization of the original fear memory so as to allow for retrospective amnesia to be achieved. This is of importance, because in practice it is often not possible to identify or recreate the situation in which fear was originally acquired (such as the exact circumstances of a traumatic event). Theoretically, in a Pavlovian conditioning situation, if the GS used for memory retrieval elicits a sufficiently strong fear response (indicative of a strong expectation of the US), omission of the US should trigger a clear prediction error, which should allow destabilizing the retrieved fear memory. However,

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the extinction findings reviewed in the previous paragraph suggest that even when a GS elicits just as strong an anticipation of the US as the original CS, it is not quite as effective in producing generalized extinction learning as that CS; CSs and GSs may thus not be functionally equivalent even if they both retrieve the fear memory to the same extent.

Empirical evidence on this issue is very limited so far. In recent work in rats, we have found that the administration of an amnestic agent after the presentation of a GS to retrieve a previously established fear memory will result in amnesia for the GS, but not for the original CS; in contrast, administration of the same amnestic agent after the presentation of the CS during memory retrieval results in amnesia for the CS as well as the GS (JM Alfei, RI Ferrer Monti, L Luyten, D De Bundel, VA Molina, T Beckers, manuscript submitted for publication). This finding represents somewhat of a challenge for the notion that memory destabilization is a mere function of memory retrieval accompanied by expectancy violation, because the GS elicited just as strong a fear response during memory retrieval as the CS (indicating that the fear memory was retrieved to the same extent by both) and the anticipation of the US was violated to the same extent as well.

In a recent study in humans, on the other hand, we have demonstrated that if category-level processing of a visual CS is encouraged during encoding of a fear memory (but not if instance-level processing is encouraged), pharmacologically-induced amnesia can be achieved by presenting the verbal category label rather than the actual CS to retrieve the fear memory (Soeter & Kindt, 2015b). In particular, if during fear conditioning on day 1, a picture of a spider was paired with shock and a picture of a snake was not, presentation of the word “spider” on day 2 accompanied by propranolol administration prevented fear responding to the spider picture on day 3; this was not the case if two different spiders had been used rather than a spider and a snake during initial fear conditioning. This observation suggests that how an emotional memory is initially encoded may critically determine whether it can later successfully be destabilized using a GS for retrieval.

Other factors may represent challenges to the translation of reconsolidation interference to clinical practice as well. For one thing, not all memories may be equally susceptible to destabilization, and in this respect, there might be quite a gap between memories that are typically created in the lab and especially the traumatic memories of individuals with PTSD. Particularly in humans, the aversive memories that are subjected to reconsolidation interference in the lab are typically recent, relatively mild and controllable (e.g., a mild electric shock, emotional pictures). Real-life traumatic experiences are characterized by rather stronger emotional memories that are established and retrieved under high levels of stress. Moreover, at the time of treatment, the traumatic experience may not be recent. It has been argued that older memory traces may be less prone to destabilization than more recent ones, perhaps because repeated intermediate instances of destabilization and reconsolidation can cause a gradual increase in memory strength (Alberini 2011). If stronger and older memories were indeed resistant to change, this would seriously reduce the feasibility of using reconsolidation interference as a tool for therapeutic forgetting. However, animal research has repeatedly indicated that amnesia can be induced for recent and remote memories alike (e.g., Debiec et al. 2002; Debiec & LeDoux 2004), and recent evidence suggests that also in humans, older memories can be made unstable (Steinfurth et al. 2014).

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Moreover, although noradrenergic enhancement of memory strength during initial consolidation increases fear generalization and slows down extinction of fear responding, it does not reduce sensitivity to pharmacological reconsolidation interference (Soeter & Kindt 2012b). The age or strength of an emotional memory trace as such may therefore not represent a principled constraint on the possibility to induce post-retrieval amnesia for that memory, although they may necessitate adjustment to the parameters of memory retrieval to induce destabilization (Suzuki et al. 2004; Wang et al. 2009).

Other characteristics of traumatic memories may pose a more serious challenge. In particular, the degree of activity of the glucocorticoid stress system during memory formation may critically determine whether later memory destabilization can be achieved. Animal research has shown that stress induction before memory acquisition can impair the later sensitivity of memory to pharmacological reconsolidation interference (Bustos et al. 2010; Hoffman et al. 2015); those effects are likely mediated by the glucocorticoid system (Cordero et al. 2003). Stress and the concomitant enhanced activity of the glucocorticoid system moreover decrease cue-elicited memory retrieval (Atsak et al. 2012; Schutsky et al. 2011), providing a further route through which stress may reduce memory destabilization. Those observations have obvious relevance for PTSD, not only because traumatic memories are particularly distressing, but also because studies have revealed glucocorticoid dysregulations in individuals with PTSD, including elevated cortisol levels in anticipation of and during presentation of stressful trauma-related cues relative to trauma-exposed individuals without PTSD (Elzinga et al. 2003) and enhanced cortisol levels during a cognitive stress challenge relative to healthy controls (Bremner et al. 2003). Those findings suggest that the reactivation and destabilization of trauma-related memories in individuals with PTSD may be particularly challenging. If so, reconsolidation interference may be more difficult to achieve in PTSD than in other anxiety disorders such as phobia. A major challenge and the topic of on-going work in our lab is how the sensitivity of stress-enhanced emotional memories to destabilization can be restored.

Capitalizing on the dynamic nature of emotional memory: Unique opportunities for novel interventions afforded by memory reconsolidation

Above we have argued that generalization poses a considerable challenge for the application of reconsolidation interference as a clinical intervention. Conversely, however, the phenomenon of reconsolidation may confer unique opportunities beyond the induction of amnesia, in particular for the reduction of generalization, that have not been widely recognized so far.

As noted above, much of the suffering caused by emotional memories is not due to the fact that those memories exist, but to the tendency for those memories to come to mind too easily, such as when the encounter with any dark-haired man triggers the retrieval of a traumatic incident involving one specific individual. Perhaps then a more appropriate goal for intervention than the induction of amnesia for the traumatic incident or the elimination of fear for that particular individual would be the prevention of excessive generalization. One potential approach for this might be to try to increase the contextualization of emotional memory. One of the factors that determines how readily emotional memories are retrieved in

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a context different from the context of encoding, is activity of the stress system during encoding (Van Ast et al. 2013): Administration of 10 mg hydrocortisone shortly before a word-learning task renders the later retrieval of emotional words less context-dependent, whereas administration of the same dose of hydrocortisone several hours before encoding has the opposite effect, compared to placebo. This effect is not observed for neutral words. This effect is likely due to effects of cortisol on contextual processing by the hippocampus (Joëls & Baram 2009). Cortisol also mediates the effect of a stress induction task before word-list encoding on the context-dependency of later retrieval (van Ast et al. 2014). We recently leveraged this phenomenon to enhance the context-dependency of memory retrieval by means of a stress manipulation not during encoding but during reconsolidation of episodic emotional memory (Bos et al. 2014a): Participants were first asked to learn two lists of emotion words against a specific background. One day later, one of the word lists was reactivated, after which the participants were subjected to a stress induction task or a control task. On a word stem completion task administered one day later, participants in the stress group exhibited enhanced contextual dependence of word retrieval for the reactivated words relative to the participants in the control group; the degree of contextual dependency of emotional word retrieval in the stress group was mediated by the strength of the cortisol response elicited by the stress induction task. An important task for future research is to determine whether similar results can be obtained for more self-relevant emotional memories (e.g., conditioned fear responses).

An approach that is only slightly different and even more preliminary is to try to increase the specificity of emotional memory representations during reconsolidation. Above we have explained that the excessive generalization of fear responses from cues that are genuinely threatening to perceptually similar cues that are actually safe is a major factor in the development of clinical anxiety. The specificity with which a fear memory is encoded has been shown to rely on dopaminergic signaling in the extended amygdala during consolidation (De Bundel et al. 2016): If mice are trained that a CS_A is followed by shock whereas a CS_B is not, pharmacological blockade of D2 dopamine receptors immediately after fear learning using systemic administration of raclopride enhances the generalization of conditioned fear responding from CS_A to CS_B on a subsequent retrieval test. Stimulation of D2 receptors using quinpirole during consolidation has the opposite effect of enhancing the discrimination between both CSs and reducing fear responding to CS_B. In a recent pilot study, we have collected preliminary data that suggest that the generalization of conditioned fear responses can also be affected by modulating dopaminergic signaling after memory reactivation rather than initial encoding (D De Bundel, T Beckers, unpublished observations).

Like the findings on contextualization of emotional memory, these results await further corroboration and clinical translation. Nonetheless, collectively they represent important first steps in what might turn out to be a breakthrough approach for constraining generalization of emotional memories and reducing their iatrogenic effects, exploiting the phenomenon of reconsolidation without inducing outright amnesia.

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Conclusion: A Brighter Future Ahead

The demonstration that the reconsolidation of emotional memory can be interfered with in humans has attracted considerable interest from basic and clinical researchers looking for ways to reduce the mental burden imposed by excessive emotional memories. While the translation from the lab to the clinic has not been an unequivocal success so far, some findings from clinical research give reason for great optimism, and recent basic research provides ample clues that can help to shed light on some of the failures. Lab findings also give indications for avenues toward further progress and possibilities for novel treatment targets beyond amnesia. We have good hopes that concerted basic and clinical research will allow steady and substantial progress in the treatment of all mental health problems in which emotional memories play a critical role.

Of particular clinical relevance is also to achieve greater closure on the mechanisms that underpin post-retrieval amnesia, that is, whether amnestic interventions after memory reactivation result in erasure of the engram in particular brain regions, thereby stripping a declarative memory from its emotional connotation, or rather result in strong retrieval interference by making memories strongly state-dependent. However, while the clinical implications of various explanations for reconsolidation interference may be slightly different, none of them would radically subtract from its clinical potential. Erasing the engram obviously makes for a more permanent and radical intervention than making retrieval state-dependent. However, rendering memory access strongly state-dependent, such that it is not retrieved but under very specific circumstances, may be a perfectly reasonable therapeutic target as well.

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Summary Points and Future Issues

- Experimental research in animals and humans demonstrates how amnesia for previously established emotional memories can be induced, using a variety of methods including biological, pharmacological, cognitive and behavioral techniques
- Such reconsolidation interference holds great potential for the development of novel, more durable and effective interventions for the treatment of psychological disorders in which emotional memories play a central etiological or perpetuating role, yet findings from clinical trials aimed at inducing amnesia for the treatment of anxiety disorders and addiction have yielded mixed results so far
- An optimal level of surprise or expectancy violation during retrieval may be a crucial factor in determining whether an emotional memory becomes sensitive to the induction of amnesia
- The use of generalization stimuli for memory retrieval may limit the efficacy of amnesia induction. Also, inducing amnesia may be particularly challenging for traumatic memories that are accompanied by high levels of stress during encoding and retrieval
- Retrieval-provoked destabilization of emotional memories may confer possibilities for intervention beyond the induction of amnesia, such as the enhancement of memory contextualization and the reduction of generalization
- The successful clinical application of reconsolidation interference will require not only further basic science but also careful investigation of how essential concepts and insights from basic science can be translated into treatment
- A better grasp on the mechanisms that underlie the induction of post-retrieval amnesia will allow a fuller understanding of its clinical implications

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Sidebar: How desirable is the spotless mind?

In recent years, debate has arisen regarding the ethical implications of memory modification. In particular, concerns have been voiced as to how desirable of a therapeutic goal it is to make people forget about significant events that have happened in their personal lives and that may play a central role in defining who they are (President's Council on Bioethics (US) 2003). Forgetting about a traumatic incident that happened fortuitously may be beneficial, but many memories may well be important to hold on to, even if they are painful (e.g., sexual abuse by a family member or a traffic accident caused by one's own recklessness). It bears mentioning, however, that the most promising reconsolidation-based intervention in humans at present, which relies on the disruption of noradrenergic signaling during reconsolidation, blocks the later recall of emotional aspects of memory only, without impairing declarative knowledge for the events involved (see section Turning back (in) time: Inducing post-retrieval amnesia for emotional memories). Also, memories are naturally dynamic, and therefore memory modification is not quite as artificial or exceptional as it may seem (Otis et al. 2015). In fact, standard treatments for emotional disorders typically serve to modify our emotional memories for the events that are involved in one way or another as well (be it by making our emotional memories harder to retrieve, by changing the personal narrative that accompanies them, by changing our emotional appraisals or through other means). All this should serve to assuage apocalyptic visions of "forgetting therapy". Eventually, as for any intervention, the degree to which the intensity of the emotional memory is dysfunctional and unwarranted will be an important criterion in deciding whether an intervention is ethically desirable; most people would likely agree that attenuating emotional memory is ethical and humane when the suffering it causes is debilitating or disproportionate to its trigger (as occurs with PTSD). Likewise, many would object to the use of memory modification interventions to blunt emotional responses that are entirely appropriate (such as the guilt that accompanies the inflicting of deliberate harm to others). In between those two is bound to remain a zone of ambiguity that will be cause for eternal discussion (Parens 2010). For an in-depth discussion of the ethical issues involved in memory manipulation, see Elsey & Kindt 2016.