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Translational Approaches Targeting Reconsolidation

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Abstract

Maladaptive learned responses and memories contribute to psychiatric disorders that constitute a significant socio-economic burden. Primary treatment methods teach patients to inhibit maladaptive responses, but do not get rid of the memory itself, which explains why many patients experience a return of symptoms even after initially successful treatment. This highlights the need to discover more persistent and robust techniques to diminish maladaptive learned behaviours. One potentially promising approach is to alter the original memory, as opposed to inhibiting it, by targeting memory reconsolidation. Recent research shows that reactivating an old memory results in a period of memory flexibility and requires restorage, or reconsolidation, for the memory to persist. This reconsolidation period allows a window for modification of a specific old memory. Renewal of memory flexibility following reactivation holds great clinical potential as it enables targeting reconsolidation and changing of specific learned responses and memories that contribute to maladaptive mental states and behaviours. Here, we will review translational research on non-human animals, healthy human subjects, and clinical populations aimed at altering memories by targeting reconsolidation using biological treatments (electrical stimulation, noradrenergic antagonists) or behavioural interference (reactivation–extinction paradigm). Both approaches have been used successfully to modify aversive and appetitive memories, yet effectiveness in treating clinical populations has been limited. We will discuss that memory flexibility depends on the type of memory tested and the brain regions that underlie specific types of memory. Further, when and how we can most effectively reactivate a memory and induce flexibility is largely unclear. Finally, the development of drugs that can target reconsolidation and are safe for use in humans would optimize cross-species translations. Increasing the understanding of the mechanism and limitations

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of memory flexibility upon reactivation should help optimize efficacy of treatments for psychiatric patients.

Keywords

Memory; Emotions; Reconsolidation; Translational approaches; Aversive conditioning; Appetitive conditioning; Norepinephrine Beta-blockers; Reactivation-extinction

1 Introduction

Maladaptive learned responses and memories contribute to psychiatric disorders, which rank among the leading causes of disability worldwide, significantly contributing to the global disease burden (WHO 2011). A primary treatment for anxiety, stress-related, or addiction disorders is exposure therapy, which is based on the principles of extinction learning in Pavlovian conditioning (Morrison and Ressler 2014; Vervliet et al. 2013). For example, in Pavlovian threat conditioning, when a neutral stimulus, such as a tone (the conditioned stimulus or CS), is paired with an aversive event, such as a shock (the unconditioned stimulus or US), the tone itself may come to elicit a range of defensive responses, such as freezing or autonomic arousal (the conditioned response or CR). Extinction refers to the gradual decrease of conditioned responses to a CS when it is repeatedly presented without reinforcement. As Pavlov first suggested (Pavlov 1927), extinction does not represent unlearning of the original memory, but rather is thought to result in a novel memory trace that comes to inhibit the expression of the initial memory. One limitation of extinction is that because the original threat memory is not altered, only inhibited, maladaptive defensive behaviours can return following the passage of time (spontaneous recovery), alterations in context (renewal), and stress (reinstatement). This poses a serious challenge to exposure-based therapies after which many patients experience a return of symptoms even after initially successful treatment (Morrison and Ressler 2014; Vervliet et al. 2013).

This potential for memory recovery even after extensive extinction training or exposure therapy highlights the need to discover more persistent and robust techniques to diminish maladaptive learned behaviours. One potentially promising approach is to alter the original memory, as opposed to inhibiting it, by targeting memory reconsolidation. The traditional view of memory suggests that that following an initial consolidation period, memories are stable and ‘fixed’ in the brain and original memory traces remain essentially unchanged (Dudai 2004; McGaugh 2000; Müller and Pilzecker 1900). Research on reconsolidation has challenged the traditional view of memory by demonstrating that reactivating previously consolidated memories can induce renewed flexibility and an opportunity to alter the original memory long after initial learning (Alberini and LeDoux 2013; Kroes and Fernández 2012; Nader et al. 2000; Schiller and Phelps 2011). This leads to the intriguing possibility that an understanding of this persistent, flexible nature of memory will enable targeting and changing specific learned responses and memories that contribute to maladaptive mental states and behaviours.

Manipulations aimed at affecting reconsolidation have used both biological (e.g. electrical stimulation of the brain, administration of pharmacological compounds) and behavioural

interventions to target reconsolidation, thus persistently altering the previously consolidated original memory following memory reactivation. In this review, we will focus on these two classes of techniques, specifically highlighting approaches that emerged from non-human animal studies and that have been applied in both healthy humans and clinical populations. First, we will discuss the discovery of reconsolidation and the criteria generated from non-human animal studies to provide convincing evidence for reconsolidation. Next, we will describe studies using electrical or pharmacological manipulations to target reconsolidation, with a specific focus on beta-adrenergic blockers. We will then review behavioural interference studies aimed at altering memory reconsolidation, with specific attention for the reactivation–extinction paradigm. For each method, we will discuss findings from studies with non-human animals, followed by preclinical studies with healthy human subjects and translational studies in clinical populations.

Finally, despite the great clinical potential, attempts to target reconsolidation to treat psychiatric disorders have had limited success. We will review potential reasons for this limited clinical efficacy and highlight future research directions that may optimize translation success. Increasing our understanding of the mechanisms underlying reconsolidation may aid to resolve the difficulties facing the translations of findings from non-human animal to patient populations and allow treatments targeting reconsolidation to live up to their clinical potential.

2 Discovering Reconsolidation

The traditional view of memory suggests that upon learning memories are initially unstable and sensitive to disturbances but stabilize over time during a process known as consolidation, following which memory is no longer sensitive to disruption (Dudai 2004; Duncan 1949; Gerard 1949; Glickman 1961; Hebb 1949; McGaugh 1966, 2000; Müller and Pilzecker 1900; Ribot 1882). Since the 1960s, great progress has been made in understanding the neural and molecular mechanisms that support memory consolidation and led to the general idea that consolidation was a process that occurred only once (e.g. McGaugh 2000). From a clinical perspective, this means that following consolidation the original memory can no longer be modified and treatments have to rely on new learning to train patients to cope with maladaptive behaviours. This leaves open the possibility that old maladaptive memories can return to dominate behaviour.

In the 1960s and 1970s, the traditional view of memory consolidation was challenged by reports that the application of electroconvulsive shock following retrieval of a consolidated memory led to memory impairment or amnesia (Lewis 1969; Lewis and Maher 1965; Misanin et al. 1968). In the wake of these findings, the idea that consolidation was not a one-time event, but that memories, could either be in a ‘active’ state and be sensitive to modification or in an ‘inactive state’ and be stable (Spear 1973). However, subsequent studies showed that following induced amnesia memories could spontaneously recover and be retrieved under more optimal cueing conditions, or be reinstated by pharmacological manipulations that do not involve potential for new learning, indicating that amnesia following reactivation can be due to temporary retrieval deficits and not a loss of the memory trace per se (for a review, see Sara and Hars 2006).

For these historical reasons, the flexibility of memory following reactivation did not receive much attention for the following decades. Renewed interest in this topic started with reports that blocking N-methyl-D-aspartic acid (NMDA) receptors after reactivation of well-trained spatial memory and beta-adrenergic blockade following reactivation of memory in an inhibitory avoidance task subsequently resulted in impaired performance, which was suggested to be evidence for memory reconsolidation (Przybyslawski et al. 1999; Przybyslawski and Sara 1997).

Interest in reconsolidation exploded when Nader et al. (2000) reported that protein synthesis inhibition within the lateral amygdala following the reactivation of a consolidated threat-conditioned response (CR) impaired subsequent expression of memory. The critical advancements of this study were that protein synthesis, known to be important for neural plasticity and memory, was inhibited within the neural circuit critical to initial consolidation and storage of conditioned threat memory (LeDoux 2000). In addition, Nader et al. (2000) showed that short-term memory was intact immediately following memory reactivation and drug administration and that the impairment took time to develop, indicating the existence of a time-dependent process following reactivation (i.e. reconsolidation). Finally, the researchers were not able to recover the expression of the original threat memory, indicating that the memory impairment was not likely due to a temporary retrieval problem. The finding that disrupting protein synthesis following reactivation can impair consolidated memories was subsequently replicated in a wide variety of species and for a wide variety of mnemonic tasks (for reviews, see Alberini 2005; Alberini and LeDoux 2013; Dudai 2004; Nader and Hardt 2009). Together these findings hold great clinical promise as they suggest that reconsolidation can be targeted to modify original maladaptive memories and behavioural responses that contribute to psychiatric disorders.

3 Criteria to Demonstrate Reconsolidation

Based on this initial research from studies with non-human animal studies, specific criteria have been generated to demonstrate that reconsolidation has been disrupted: (1) a previously consolidated memory must be reactivated by a reminder cue. (2) The manipulation aimed at altering reconsolidation should ideally be provided post-reactivation, rather than pre-reactivation. (3) Memory should be affected after a time window allowing reconsolidation to take place rather than immediately (i.e. short-term memory is intact), in line with reconsolidation being a time-dependent process (Dudai and Eisenberg 2004; Nadel and Land 2000; Nader et al. 2000; Przybyslawski and Sara 1997). A more contested criterion is that (4) the impairment should not be attributable to retrieval failure or a reactivation-locked, temporary inability to access memory traces that dissipate over time (Lattal and Abel 2004). Hence, memory should not spontaneously recover after longer delay periods or under different cueing conditions (Sara and Hars 2006). The reason this latter criterion is contested is that impairing reconsolidation may result in an attenuation of memory, not a full loss, leaving open the possibility of at least partial recovery.

4 Biological Interventions Targeting Reconsolidation

4.1 Electrical Stimulation

The first studies showing disturbance of previously consolidated memories following reactivation used electrical stimulation of the brain to evoke generalized seizure activity in non-human animals (Lewis 1969; Lewis and Maher 1965; Misanin et al. 1968). Electroconvulsive stimulation is thought to disturb normal ongoing neural activity that contributes to memory formation. The effect of electroconvulsive stimulation on disrupting previously consolidated reactivated memories in humans can be studied in depressed patients receiving this as a treatment for their psychiatric condition. In spite of the success of initial studies in non-human animals, the first attempt to use electroconvulsive therapy (ECT) to disrupt memory for a previously consolidated, reactivated memory in humans was not successful for either item or paired associative episodic memory (Squire et al. 1976). This study also found limited effects of ECT on the initial consolidation of episodic memory, suggesting that the protocol may have lacked sensitivity to detect changes in memory. In addition, in this initial study, memory was tested 6–10 h after reactivation and ECT and effects on reconsolidation may take a longer time to become apparent. More recently, it has been demonstrated that ECT following episodic memory reactivation caused a time-dependent and reactivation-specific memory impairment in humans (Kroes et al. 2014), meeting critical criteria to demonstrate reconsolidation in humans. With this in mind, it is interesting to note that an early clinical report suggested that the application of ECT immediately following patients acting out their compulsions or experiencing hallucinations resulted in a long-term absence of symptoms (Rubin et al. 1969).

Intriguingly, another technique thought to manipulate electrical activity in the brain in a more localized manner has also been suggested to alter reactivated memories in humans. Stimulation of the prefrontal cortex with transcranial magnetic stimulation (TMS) was found to cause a time-dependent enhancement of reactivated memory for word lists (Sandrini et al. 2013). However, the same group also reported that transcranial direct current stimulation (tDCS) of the same region resulted in memory enhancement for both reactivated and non-reactivated words (Sandrini et al. 2014). The mechanisms underlying this enhancement effect are currently unclear, and any applications for patients remain to be tested.

Overall, evidence suggests that ECT can impair reactivated episodic memory in a time-dependent manner, and local electrical stimulation of the brain may enhance reactivated memory. The use of ECT to target reconsolidation is highly invasive limiting its clinical applicability, although relatively less invasive techniques, such as TMS, may hold some promise. In the following paragraphs, we will focus on studies combining memory reactivation with pharmacological manipulations or behavioural interference techniques that are more likely to have translational significance. Although several chemical manipulations have been used to disrupt reconsolidation in non-human animals, most notably protein synthesis or protein kinase inhibitors, which present safety challenges for human use, we will specifically focus on noradrenergic manipulations as these have been used in studies with non-human animals, in human preclinical studies, and in patient populations.

4.2 Noradrenergic Manipulations Targeting Reconsolidation: Non-human Animal Studies

Pharmacological manipulations of the noradrenergic system have been used to target reconsolidation in order to modify both reactivated aversive memories and appetitive memories. The effectiveness of altering threat-related responses by noradrenergic manipulations following memory reactivation appears to vary depending on the memory task (Alberini 2011). Studies using aversive cue conditioning and contextual cue conditioning have reported that blocking norepinephrine using propranolol systemically or within the amygdala following memory reactivation results in attenuated threat-related defensive responses of recent and remote memories (Dębiec et al. 2011; Debiec and Ledoux 2004; Gamache et al. 2012; Muravieva and Alberini 2010), consistent with a role for norepinephrine in the reconsolidation of aversive cue-conditioned memories. Studies using pure context conditioning, i.e. where the onset of an aversive outcome (US) is not signalled by a specific cue, found that enhancing noradrenergic functioning following memory reactivation increases subsequent freezing, but systemic administration of propranolol following reactivation had only a modest effect on attenuating threat-related contextual conditioning (Abrari et al. 2008; Gazarini et al. 2013).

Studies using aversive inhibitory avoidance tasks have produced contradictory results, with some finding that blocking norepinephrine following memory reactivation reduces avoidance behaviour (Do Monte et al. 2013; Przybyslawski et al. 1999), and others failed to find such an effect (Muravieva and Alberini 2010). The latter researchers directly compared the effect of blocking norepinephrine on aversive cue-conditioning and inhibitory avoidance tasks (Muravieva and Alberini 2010). Noradrenergic blockade following memory reactivation was found to attenuate freezing in the cue-conditioning task. Specifically, the authors found that blocking norepinephrine following memory reactivation with the CS (tone) in the original context resulted in reduced subsequent freezing in response to both the CS and the context, whereas reactivating memory by the context alone only reduced subsequent freezing to the context, but not the CS (Muravieva and Alberini 2010). Following inhibitory avoidance training, rodents exhibit both freezing and avoidance behaviour on subsequent tests. Although noradrenergic blockade reduced retrieval, it did not seem to disrupt reconsolidation of avoidance behaviour, which was intact, but it did attenuate freezing behaviour (Muravieva and Alberini 2010). Finally, administration of the alpha-1 noradrenergic antagonists prazosin systemically or within the pre-limbic cortex, but not the anterior cingulate cortex, following memory reactivation was found to attenuate avoidance behaviour (Do Monte et al. 2013). Memory research over the last century has recognized that different forms of behavioural expression involve distinct neural systems that represent specific types of memory (Fuster 2009; Henke 2010; Squire 1992; Tulving 1972). Of relevance here is that conditioned freezing responses depend on the amygdala (Davis and Whalen 2001; Fanselow and Poulos 2005; Herry and Johansen 2014; LeDoux 2000), whereas place avoidance behaviour involves the hippocampus, striatum, and neocortex (Ambrogi Lorenzini et al. 1997, 1999; Fendt and Fanselow 1999; Izquierdo et al. 1997; McGaugh 2004; McIntyre et al. 2003). These findings suggest that different neural systems that give rise to memory expressed as distinct types of behaviours may vary in sensitivity to modification by noradrenergic antagonists following retrieval.

A second line of research has focused on the modification of reactivated appetitive memories. Two tasks have mainly been used: self-administration (SA), in which an animal learns to make an operant response following a cue that leads to administration of a stimulant, such as cocaine, morphine, or alcohol, and conditioned place preference (CPP) where an animal comes to prefer the spatial location where it has received a stimulant. The acquisition of these appetitive conditioned responses depends on the ventral tegmental area, striatum, amygdala, and, for contextual information, the hippocampus (Everitt 2014; Everitt and Robbins 2005; Robbins et al. 2008). Memory reactivation combined with noradrenergic antagonists has been reported to reduce self-administration behaviour of cocaine and sucrose but may be more limited for alcohol (Diergaarde et al. 2006; Milton et al. 2008; Williams and Harding 2014; Wouda et al. 2010). In addition, studies have reported an attenuation of CPP by beta-blockers following memory reactivation (Bernardi et al. 2006, 2009; Fricks-Gleason and Marshall 2008; Robinson and Franklin 2007), although effects have not always been equally strong in that memory has been found to recover over time (Fricks-Gleason and Marshall 2008; Robinson and Franklin 2007), and more remote memories may be more resistant to modification (Robinson and Franklin 2010; Robinson et al. 2011). Note that many of the memories in these tasks are somewhat more remote as training procedures often take 1 week or more. Interestingly, repeatedly reactivating memory combined with noradrenergic treatment was found to attenuate more remote memories and prevent recovery (Fricks-Gleason and Marshall 2008). Understanding the mechanism through which noradrenergic manipulations may affect reactivated appetitive memories is complicated by the fact that several studies have given noradrenergic blockers well before memory reactivation, which lack no reactivation control conditions, and most studies have used very long reactivation times. Studies in the aversive memory domain have found that short memory reactivation results in reconsolidation, but longer reactivation trials result in extinction learning (Eisenberg et al. 2003; Pedreira and Maldonado 2003; Suzuki et al. 2004), which leaves open possible alternative interpretations for the attenuation of reactivated appetitive responses by noradrenergic blockade such as enhancing extinction, as opposed to disrupting reconsolidation. In a series of experiments, noradrenergic antagonists applied systemically prior to memory reactivation were found to cause a sustained impairment of the retrieval, but not reconsolidation, of cocaine CPP (Otis et al. 2013, 2014; Otis and Mueller 2011). This sustained retrieval impairment was found to depend on noradrenergic functioning in the prelimbic cortex and hippocampus (Otis et al. 2013, 2014). The injection of propranolol within the amygdala did not affect retrieval but did impair memory on subsequent tests in line with an impairment of reconsolidation (Bernardi et al. 2009; Otis et al. 2013). Collectively these studies indicate that combining memory reactivation with noradrenergic antagonists can reduce appetitive responses. It is less clear whether alterations in memory are the result of impaired reconsolidation or whether other mnemonic processes may also contribute to the attenuation of learned responses.

In summary, rodent studies have found that noradrenergic antagonists can attenuate reactivated aversive and appetitive memories. Yet not all memory types appear equally sensitive to reactivation-dependent flexibility. The dependence of memory on specific brain regions and its change over time with systems consolidation (Alvarez and Squire 1994; Frankland and Bontempi 2005; Marr 1971; Nadel and Moscovitch 1997; Squire 1992)

appear to limit renewed flexibility. Further, noradrenergic antagonists may affect other mnemonic processes that can also lead to attenuation of learned responses, such as retrieval or extinction. Noradrenergic antagonists are at best indirect effectors of protein synthesis, but a discussion of the molecular mechanisms through which noradrenergic antagonists may assert their effects on reactivated memories is outside the scope of this chapter (for review, see Otis et al. 2015).

4.3 Noradrenergic Manipulations Targeting Reconsolidation: Preclinical Human Studies

Most studies targeting reconsolidation using pharmacological manipulations in humans have used the noradrenergic antagonist propranolol, as this is one of the few drugs used in non-human animal studies targeting reconsolidation that is safe for use in humans. Mirroring findings from non-human animals, human studies using propranolol to target reconsolidation are finding that not all types of memories are affected equally. A complicating factor in understanding how noradrenergic antagonists may alter reactivated memories in humans is that in majority of studies, the drug propranolol has been given prior to memory reactivation violating the second criterion to demonstrate reconsolidation. The reason for this is that following oral administration of propranolol, it takes 60–90 min for the drug to take effect and researchers have suggested that post-reactivation administration may miss the critical window to affect memory flexibility. Because of this, the impact of the drug on retrieval processes cannot be ruled out. Moreover, because propranolol is relatively long acting, no study has assessed possible memory alterations shortly after reactivation of drug administration (i.e. intact short-term memory), because the drug would still be active. Given this, most of these studies do not meet the second and third criteria to demonstrate reconsolidation described above. Nevertheless, an increasing body of work indicates that combining reactivation with propranolol can diminish some learned threat-related responses in humans.

The first indication that noradrenergic antagonists may attenuate reactivated memories in humans came from a study using aversive threat conditioning (Miller et al. 2004). In this study, three groups of subjects were conditioned to two visual stimuli of which one (CS+) was occasionally followed by a mild electrical shock to the wrists (US) and the other visual stimulus was never followed by a shock (CS−). Skin conductance responses (SCR), an indication of autonomic arousal, served as an index of threat-related responses. A day later, memory was reactivated by a single presentation of the CS+ and CS− and either followed by administration of the noradrenergic antagonist propranolol or placebo. A third group did not receive memory reactivation but did receive propranolol. When tested after 24 h, the group that received memory reactivation and placebo showed greater SCR to the CS+ than CS− on the first trial of the recovery test, whereas the group who received memory reactivation followed by propranolol administration did not show differential responses to the CS+ and CS− on the first trial of the test session. Although this result was encouraging, there are several aspects of the data that were problematic. First, the group that did not receive memory reactivation but was administered propranolol also did not show differential responses to the CS+ and CS− on the first trial of the test session. Second, the absence of differential responses in both propranolol groups was partially driven by increased responses to the CS− at test. Third, the lack of differential responses was limited to the first trial at test

and both drug groups showed greater responses to the CS+ than CS− on subsequent trials. These results indicate not a general reduction in defensive responses but a temporary inability to discriminate between two stimuli. Finally, this effect was only present in female participants. These initial results indicate that while propranolol administered post-reactivation in human may have some effect on later expression of learned defensive responses, the effect is more limited than findings with non-human animals. It has been suggested that one possible reason for the return of conditioned defensive responses in later trials of the recovery test may be due to intact episodic knowledge of the CS–US contingencies that can drive the expression of conditioned responses in humans without reinforcement (Olsson and Phelps 2007; Phelps et al. 2001; Raio et al. 2012).

In a series of publications, Kindt and colleagues showed that administering propranolol before or after memory reactivation can decrease threat-potentiated startle responses (Kindt et al. 2009; Sevenster et al. 2012, 2013, 2014; Soeter and Kindt 2010, 2011, 2012). In these studies, subjects learn that a cue is predictive of a mild electrical shock, while another cue is never followed by a shock. Throughout the task, the startle eyeblink response to loud white noise bursts is measured. As subjects learn which cue predicts the occurrence of the shock, the magnitude of their eyeblink response to the noise burst is greater when the threatening stimulus is also presented (Grillon et al. 1991). In addition, Kindt and colleagues measured SCR and had subjects rate their expectancy of the occurrence of a shock on each trail as an online measure of explicit knowledge of the contingencies. The combination of memory reactivation and propranolol administration attenuated threat-potentiated startle responses 1 day later, but did not attenuate SCR or expectancy ratings. Propranolol without memory reactivation or memory reactivation combined with placebo had no effects. Further, the researchers were unable to reinstate the threat-potentiated startle responses (Kindt et al. 2009). In a follow-up study, the response was not found to spontaneously recover after longer delays (Soeter and Kindt 2010). These results mirror findings in non-human animals, but demonstrate that not all types of threat memory expression are equally affected by beta-blockade at memory retrieval (Alberini 2011).

It is interesting to speculate on the reason why Miller and colleagues found that propranolol temporarily attenuated reactivated aversive memory using SCR, but Kindt and colleagues found that propranolol only reduced startle responses but left threat-related SCR and explicit knowledge of the aversive events intact. It has been suggested that startle is a more direct measure of amygdala-dependent memory than SCR, the latter being an index of more explicit memory (Kindt et al. 2009). However, threat-conditioned SCR can be acquired even in the complete absence of awareness of the predictive cues (Ohman and Soares 1994; Raio et al. 2012; Schultz and Helmstetter 2010), rendering this explanation unlikely in our opinion. Both threat-conditioned SCR and startle responses involve the human amygdala at acquisition (Bechara et al. 1995; Klumpers et al. 2014; LaBar et al. 1998), and expression of both is correlated with dorsomedial prefrontal cortical activity (Klumpers et al., online prepublication). An important difference is that SCR is measured as an anticipatory response in the absence of an aversive event, but startle is measured in response to an actual aversive event (loud noise) that is enhanced by the anticipation of threat. Threat-potentiated startle thus effectively measures an emotional enhancement of a response to threat itself, and propranolol at reactivation eliminates the enhancement effect. Further, the simultaneous

measurement of startle and SCR using long CS presentation times might not be optimal to assess SCR. In threat-conditioning tasks, the SCR is a phasic response to the anticipation of threat that initially occurs to the onset of a predictive cue but over learning shifts in time to the offset of the cue when the shock is expected to occur. Often at the end of threat conditioning, peak of the response occurs well after the onset of the cue and would be overshadowed by the occurrence of noise bursts or shocks if those were present at the end of a trial. Yet a study optimized to measure SCR and following the procedures of Kindt et al. (2009) also found no effect of reactivation and propranolol on subsequent SCR although it lacked an appropriate placebo control condition (Spring et al. 2015). Another important difference may be that Kindt and colleagues use higher reinforcement rates than Miller and colleagues did. In human threat conditioning, partial reinforcement rates are generally used because higher reinforcement rates result in very rapid extinction learning if threat-predictive cues are not reinforced in subsequent test sessions (Capaldi et al. 1970; LaBar et al. 1998; Phelps et al. 2004). An additional difference is the explicitness of task instructions. Whereas most human conditioning studies instruct subjects that ‘there is a relationship between the cues and the shocks’, Kindt and colleagues instruct subjects that ‘one of the cues will be followed by a shock in most of the cases, whereas the other cue would never be followed by the shock’. In the latter case, based on explicit knowledge, learning which stimulus predicts shock and which does not can be fully learned on the first reinforced trial. Such rapid learning resulting from explicit knowledge may comprise a different neural circuitry than that which supports reinforcement learning over multiple trials. Finally, probing online expectancy judgement may affect autonomic threat-related responses (Warren et al. 2014). Explicit knowledge of contingencies gained from episodic experience or instructions affects both skin conductance and startle responses and may result in changes in the involvement of the amygdala, hippocampus, and medial prefrontal cortex in threat-related responses (Bechara 1995; Coppens et al. 2009; Funayama et al. 2001; Phelps et al. 2001; Tabbert et al. 2006). With this in mind, it is interesting that if the shock electrodes were not attached at the time of memory reactivation, propranolol administration did not reduce subsequent threat-potentiated startle responses (Sevenster et al. 2012). These findings highlight the influence of episodic memory and explicit knowledge on the reactivation of implicit sympathetic and startle responses in humans. From a clinical perspective, it is also interesting that higher trait anxiety has been reported to limit the effectiveness of memory reactivation and propranolol administration to attenuate threat-related responses, although this was not replicated in a later study (Bos et al. 2014; Soeter and Kindt 2013). Which differences between experiments contribute to the discrepancies in findings is unclear at the moment; however, even Kindt and colleagues were not able to replicate their own findings in two separate studies (Bos et al. 2014) highlighting that it is imperative to collectively investigate these issues if we wish to reach translational applications for patients.

As mentioned earlier, memory reactivation and propranolol administration can diminish some threat-related responses but leave an index of episodic memory intact (Kindt et al. 2009). It could be considered optimal only to reduce physiological threat responses in patients, but leave patients’ episodic memory for the events of a traumatic experience intact. However, if episodic memories contribute to the negative symptoms experienced by patients or contribute to a potential return of physiological threat-related responses, one may also

wish to alter episodic memories as well. Several studies have specifically targeted reactivated episodic memories using propranolol (Kroes et al. 2010; Schwabe et al. 2012, 2013).

The first study had participants study neutral and emotional words (Kroes et al. 2010). On day two, participants were given placebo or propranolol followed by memory reactivation by presenting the word stems (first three letters) for a subset of the emotional and neutral words and asked to recall the words. On Day 3, memory was assessed with a cued recall task in which subjects were provided word stems and asked to remember the words. Subjects who had received placebo showed a well-known emotional enhancement effect in that they were able to correctly complete more stems of emotional words than neutral words. Interestingly, propranolol abolished the emotional enhancement effect. Critically, propranolol did not diminish memory completely but specifically abolished the beneficial contribution of emotion to memory. Further, the researchers found that emotional words that were not recalled in the presence of propranolol were also unlikely to be recalled the next day. In contrast, emotional words that were correctly recalled, and thus supposedly reactivated, in the presence of propranolol were likely to still be remembered the next day. Therefore, the authors suggest that the attenuation of memory by propranolol may result from a sustained retrieval impairment and/or new learning and not necessarily be the consequence of reconsolidation disruption (Kroes et al. 2010). Two other studies studied the effect of propranolol on the reactivation of memory for neutral and emotional pictures (Schwabe et al. 2012, 2013). Both studies also found that propranolol during memory reactivation abolished the enhanced recognition of emotional pictures on day later. Propranolol without memory reactivation had no effect. Interestingly, propranolol with memory reactivation was found to specifically reduce the number of arousing pictures subjects indicated as ‘remembered’ but did not reduce the number of arousing pictures specified as ‘known’ (Schwabe et al. 2013). With ‘remember’ responses, subjects denote that they consciously recollect having seen the picture before, whereas ‘know’ responses indicate that they merely have a feeling of familiarity. Remembering has been suggested to reflect hippocampus-dependent episodic memory, whereas knowing or familiarity is proposed to rely more on parahippocampal regions (Tulving 1985). Functional magnetic resonance imaging (fMRI) data indicated amygdala and hippocampus involvement during memory reactivation in both the placebo and propranolol groups (Schwabe et al. 2012). One day later, the propranolol group displayed reduced amygdala and hippocampus responses during recognition of arousing pictures. These studies indicate that beta-blockade at reactivation may attenuate the emotional enhancement of episodic memory (Kroes et al. 2010; Schwabe et al. 2012, 2013), but it is precarious to attribute these memory impairments as evidence for reconsolidation.

In conclusion, a growing body of studies indicated that propranolol administered at the time of memory reactivation could result in a subsequent attenuation of threat-related responses and aspects of episodic memory in humans. However, given the pharmacodynamics of propranolol, it has been difficult to meet the critical criteria to demonstrate convincing evidence for reconsolidation. All preclinical studies have investigated the effect of beta-blockade on one-day-old memory. It is currently unclear whether propranolol at reactivation has an effect on more remote memories. Furthermore, the effect of propranolol on episodic memory seems to be limited to an attenuation of the emotional enhancement of episodic

memory. Considering that threat-related defensive responses involve the amygdala (LeDoux 2000) and the emotional enhancement of memory is considered to result from the amygdala modulating hippocampal processing (McGaugh 2002; Phelps 2004; Richardson et al. 2004) via a beta-adrenergic mechanism (Cahill and McGaugh 1998; McGaugh 2004; Strange and Dolan 2004), it could be that the effects of propranolol are limited to amygdala-dependent memories. The exact mechanisms through which noradrenergic blockage may affect reactivated memories will be an important question for future research. It is possible that propranolol affects reconsolidation in humans, but it is also clear that retrieval and new learning can be affected. In order to develop translational approaches, it is imperative to dissociate these mnemonic processes and understand when and how each process is evoked and how to target each process to yield optimal treatment outcomes for patients. Finally, so far all preclinical human studies have focused on the effect of beta-blockade on negative arousing memories and none on appetitive memories. Nevertheless, the findings that beta-blockade can attenuate reactivated memories have encouraged researchers to start studies in clinical populations that will be discussed next.

4.4 Noradrenergic Manipulations Targeting Reconsolidation: Studies in Clinical Populations

Translational studies targeting reconsolidation of aversive and appetitive memories with beta-blockers in clinical populations have had mixed, and limited, results. First, in a series of studies, traumatic memories of post-traumatic stress disorder (PTSD) patients were reactivated by creating a narrative script of patient's own traumatic experiences and combined with propranolol administration (Brunet et al. 2008, 2011, 2014). One week later, patients were again presented with the trauma script and mentally imagined the experience. Patients who had received propranolol had lower heart rates than those who had received placebo to a level below that normally observed in PTSD patients in this task. Skin conductance levels (note a measure reflecting overall conductance not differential responses) were also reduced in patients who had received propranolol, but not below PTSD cut-off levels. Electromyography, a third measure of arousal, was reduced in both the patients who had received propranolol and placebo (Brunet et al. 2008). The following studies replicated these results when reactivation and propranolol administration were repeated over six weekly sessions. Patients also showed a reduction of PTSD symptoms over the course of treatment and at a six-month follow-up and 70–90 % of the patients no longer meeting the criteria indicative of PTSD (Brunet et al. 2011, 2014). Conducting exploratory studies in clinical patients is demanding. Probably for this reason, the studies mentioned above were open-label, lacked placebo controls, or used patients who refused treatment (and may thus constitute a particular problematic clinical group) as comparison and did not include no reactivation control groups. Furthermore, over three independent studies, the same research group was not able to replicate the reduction in sympathetic measures or clinical symptoms in PTSD patients due to memory reactivation and propranolol administration (Wood et al. 2015). Hence, studies investigating the possibility of combining memory reactivation with propranolol to treat PTSD patients have had limited success.

Several studies have also investigated the effects of memory reactivation and propranolol on appetitive-related responses in addiction patients. The first study had heroin addicts learn 10

heroin-related positive words, 10 heroin-related negative words, and 10 neutral words (Zhao et al. 2011). The next day, subjects received propranolol or placebo and memory was reactivated by free recall of the words or memory was not reactivated. On the third day, in the absence of drug, the patients who had received propranolol and memory reactivation recalled less heroin-related positive and negative words, but similar numbers of neutral words compared to the control groups. Hence, similar to preclinical human studies (Kroes et al. 2010; Schwabe et al. 2012, 2013), propranolol and memory reactivation seem to reduce the emotional enhancement of memory. Interestingly, the reduction of memory from the first to the third day was comparable between the reactivation and propranolol administration group and no reactivation group (Zhao et al. 2011). This could indicate that propranolol blocked the enhancement of memory that can result from reactivation (Inda et al. 2011). Two other studies investigated drug craving and drug-related sympathetic responses (Pachas et al. 2014; Saladin et al. 2013). In one study, memory was reactivated by presenting cocaine addict with videos of drug paraphernalia (e.g. bags of drugs, mirrors, pipes) followed by placebo or propranolol administration. One day later, the patients who had received propranolol showed reduced blood pressure and reduced cravings, but no change in heart rate and SCR to drug-related videos (Saladin et al. 2013). Furthermore, no change in drug use was observed at follow-up on week later. In another study, nicotine addicts received propranolol or placebo and memory was reactivated via personalized smoking scripts or personal non-smoking scripts (Pachas et al. 2014). One week later, subject who had received propranolol exhibited a reduction in craving but no change in sympathetic responses to smoking scripts. However, no interaction between drug and memory reactivation was found indicating a general effect of propranolol on the reduction of cravings. In sum, studies investigating the possibility of combining memory reactivation with propranolol to treat addiction patients have also had limited success.

To conclude, translational studies targeting reconsolidation of aversive and appetitive memories with propranolol in clinical populations have had mixed and limited results. Studies have targeted reconsolidation but have had difficulty implementing important controls to meet the criteria to demonstrate reconsolidation and to demonstrate clinical effectiveness. Although several studies have had success in attenuating responses, it is unclear whether this is attributable to effects on reconsolidation or other mnemonic processes, such as exposure or extinction. In concert with findings from non-human animal and preclinical human studies, not all memory measures are equally affected by reactivation and propranolol in clinical populations. Modification of arousal-related sympathetic responses has been reported but not reductions of approach- or avoidance-related symptoms. Furthermore, the effect of propranolol on episodic memory in patients may also be limited to reducing the emotional enhancement effect. Again, this suggests that the brain regions that support the specific memory assessment may influence the effectiveness of propranolol at memory reactivation in patients. Psychiatric disorders such as PTSD and addiction are multifaceted disorders, and distinct symptoms likely involve memories dependent on different neural systems that vary in sensitivity to alteration following reactivation. Furthermore, studies in patients aimed at reducing clinical symptoms are targeting very remote memories that have had time to undergo systems consolidation. Preclinical human

studies have not addressed such remote memories, and this could be a significant limitation to translational efficacy.

4.5 Noradrenergic Manipulations Targeting Reconsolidation: Conclusions

In conclusion, studies with non-human animals, in healthy human subjects, and in clinical patient populations indicate that noradrenergic antagonists can attenuate reactivated aversive and appetitive memories. However, translational studies targeting reactivated memories with propranolol to treat symptoms of patients have had mixed and limited effects. Several limiting factors have been discussed. Not all memory types appear equally affected by reactivation and noradrenergic antagonist administration. The dependency of memories on specific brain regions and their change over time with systems consolidation might limit the possibility to alter memories. More specifically, it appears that amygdala-dependent memories such as cue-conditioned arousal responses may be attenuated by noradrenergic blockade following reactivation, but these effects are limited and difficult to replicate in humans. The ability to alter hippocampus-dependent memories such as contextual conditioned memories in non-human animals or episodic memory in humans might be limited to the emotional enhancement of memory that is possibly the result of modulation of the hippocampus by the amygdala. This could be either the consequence of intrinsic qualities of distinct brain regions, or the result of the mechanisms of action of propranolol, or a combination of both. Additionally, remote memories that have undergone systems consolidation may be an important limiting factor to alter reactivated memories with noradrenergic antagonists. Further, noradrenergic antagonists may affect reconsolidation but can also have sustained effects by influencing other mnemonic processes such as retrieval or new learning. Studies in humans have had particular difficulty in dissecting distinct effects on different potential mnemonic processes. It will be important for future studies to critically investigate the mechanisms and memory processes that can lead to alterations of reactivated memories by noradrenergic antagonists if we wish to develop optimal translation applications to treat patients.

5 Behavioural Interventions Targeting Reconsolidation: The Reactivation–Extinction Paradigm

Although pharmacological manipulations are the most common techniques to alter reconsolidation in animal models, the translation to humans to date has been limited due to ethical/safety reasons, and as outlined above, the translation of drugs safe for human use has had limited success. An alternative approach is to rely on behavioural techniques proposed to influence reconsolidation, the most prominent being the reactivation–extinction paradigm.

The notion that behavioural interventions can influence reconsolidation is based on the premise that a key function of reconsolidation might be to update older memories with new information available at the time of retrieval, thus supporting the dynamic nature of memory. The first demonstration of this effect was a study conducted in humans examining motor sequence learning (Walker et al. 2003). In this study, participants learned a motor sequence on the first day as indicated by decreased reaction time over trials. The following day, they learned another motor sequence that was, or was not, proceeded by reactivation of the earlier

acquired motor sequence. On the third day, memory of the first motor sequence was assessed. It was found that reactivation of the first motor sequence prior to learning a second motor sequence impaired its later retrieval relative to the no reactivation group. Importantly, this study is one of the few studies in humans that meet all the criteria for targeting reconsolidation described earlier and the first to demonstrate that behavioural techniques can also be used to influence reactivated memory.

The extension of the behavioural interference of reconsolidation to threat memories resulted in the reactivation–extinction paradigm. A common way to associate threatening cues with safety is through extinction training, where the threat-conditioned cue is presented repeatedly without the aversive outcome. This learning process creates a novel association of the CS with no US, which is traditionally thought to compete for expression with the threat association. If extinction training was sufficient, subsequent encounters with the CS would not trigger defensive responses, but returning to the threatening context, stressful exposure to threat or mere passage of time can trigger the expression of the initial threat association over the extinction memory. But what if extinction training were to occur during reconsolidation? Theoretically, the safety information learned through pairing the CS with the absence of a US might be incorporated into the threat association during the reconsolidation process. This is the rationale behind the retrieval extinction paradigm, a protocol that can prevent the return of the conditioned defensive responses in animals and humans.

5.1 Reactivation–Extinction: Non-human Animal Studies

The first report of the post-retrieval extinction effect in rodents (Monfils et al. 2009) used a threat-conditioning paradigm. On Day 1, rats were trained to associate a tone (CS) with electric shock (US). A day later, the rats were exposed either to one presentation of the CS without the US (reminder trial), or to the context only (no reminder). Extinction training followed, either 10 min or 1 h after the reminder trial (during reconsolidation), or 6 or 24 h after the reminder trial (when reconsolidation was complete). Another group had extinction, but no reminder trial preceded. A day later, the rats were exposed again to the CS under conditions that typically lead to the recovery of the threat memory following standard extinction. Only rats that received a reminder trial prior to extinction but before reconsolidation was complete (10 min or 1 h) did not show the recovery of the threat-related defensive freezing response (CR). These rats also showed impaired reacquisition when exposed to additional tone–shock pairings, suggesting that the original threat association was not erased but rather changed its meaning from threat to safety.

This initial finding spurred dozens of follow-up studies attempting to replicate this finding across species as well as to adapt the paradigm to reward and instrumental memories. Reports have been mixed, with many successful replications but also null or even opposite results. The vast parametric variation that these studies brought about outlines the probable boundaries of the post-retrieval extinction phenomenon. Recognizing boundary conditions is essential for the translation of these findings to clinical applications. One of the most important mediating factors is the age of the memory. The majority of animal studies thus far examined laboratory-made memories that were one to three days old (for reviews, see Auber et al. 2013; Flavell et al. 2013), whereas anxiety disorders often involve memories

that are several months or years old. One study of post-retrieval extinction of remote memories (Costanzi et al. 2011) examined a month-old contextual memory. In this study, mice learned to associate context with a foot-shock. Approximately one month later, the mice retrieved the memory when placed in the conditioning context for 3 min (no shock was delivered) and 1 h later underwent a 30-min extinction session in the same context. The memory test was conducted a day later by placing the mice back in the conditioning context and measuring their levels of freezing. There were no differences between mice that underwent post-retrieval extinction compared to mice that underwent extinction only, indicating that post-retrieval extinction failed to attenuate remote hippocampus-dependent memories that have had time to undergo systems consolidation.

A follow-up study investigated epigenetic mechanisms differentiating recent and remote memories (Graff et al. 2014). Using cued context conditioning in mice, this study showed that retrieval of recent memories induced a time-limited period of neuronal plasticity in the hippocampus, mediated in part by epigenetic modification of gene expression involving acetylation of histone proteins. By modifying chromatic compaction, histone acetylation promotes gene transcription, thereby regulating long-lasting neuronal plasticity (Levenson and Sweatt 2005). Graff and colleagues showed that retrieval of remote memories failed to generate this temporary histone acetylation-mediated neuroplasticity in the hippocampus. The pathway critical for this process is nitrosylation of histone deacetylase 2 (HDAC2) following memory retrieval, leading to dissociation of HDAC2 from the chromatin. Using HDAC inhibitors, Graff and colleagues were able to reinstate hippocampal plasticity during post-retrieval extinction of remote memories and prevent the return of the conditioned freezing responses. In the absence of memory retrieval, treatment with HDAC inhibitors had no effect, suggesting that the original memory trace might have been modified. From a clinical perspective, these findings suggest that at least for certain types of remote memories, combining pharmacological with behavioural treatment might be more beneficial than either approach alone.

These studies demonstrate that the translation of the post-retrieval extinction procedure into clinical settings would require careful consideration of timing. In addition, the age of memory, also the duration of the reminder, the time between the reminder and extinction, and the time between post-retrieval extinction and memory test might significantly influence memory attenuation. Previous studies have shown that long exposure to the CS or the conditioned context would result in extinction rather than memory reactivation (Eisenberg et al. 2003; Power et al. 2006; Suzuki et al. 2004). For example, post-retrieval extinction of context conditioning in crabs (Perez-Cuesta and Maldonado 2009) failed to prevent the return of conditioned responses when using a relatively long reminder session (15 min). As for the time between the reminder and extinction, studies utilizing Pavlovian threat conditioning found that reconsolidation lasts more than an hour, but less than 6 h, although this window may depend on the type, strength, and age of the memory (Duvarci and Nader 2004).

Another potentially important factor for clinical treatment is the social environment. A previous study that used the post-retrieval extinction effect showed memory enhancement instead of attenuation (Chan et al. 2010). There were several parametric variations in this

study compared to the original paradigm (Monfils et al. 2009), such as a different frequency of the auditory CS and a different contextual modulation. One interesting difference, though, was the housing conditions of the rats (Auber et al. 2013), which is usually overlooked. The rats in the original study were housed individually, whereas Chan and colleagues housed the rats in groups of eight. Previous studies have shown that animals respond to conspecific in distress (Panksepp and Lahvis 2011). Observing a threatened cage mate might facilitate threat learning (Knapska et al. 2010) and induce robust renewal of conditioned freezing in extinction-trained mice (Nowak et al. 2013). Such social transmission might explain the memory enhancement in the study of Chan and colleagues. Vicarious modulation of post-retrieval extinction might be an intervening factor in clinical treatments, especially those involving group dynamics.

The post-retrieval extinction paradigm has been successfully adapted to appetitive learning with implications for drug addiction (Milton and Everitt 2010). Various protocols included different positive reinforcers including sucrose (Flavell et al. 2013), grain pellets (Olshavsky et al. 2013), alcoholic beer (Millan et al. 2013), morphine, and cocaine (Ma et al. 2012; Sartor and Aston-Jones 2014; Xue et al. 2012). In contrast to Pavlovian conditioning of threat, the appetitive paradigms often involve instrumental behaviour. For example, Xue et al. (2012) trained rats to self-administer cocaine or heroin using nose poking. The drug infusions were accompanied by a light cue and a buzzing tone. The reminder consisted of a 15-min exposure to the training context, where nose poking was associated with the light and tone, but no drug was delivered. Ten minutes or 6 h later, or without the reminder, all rats underwent a 180-min extinction session, conducted similar to the reminder session. The rats repeated this retrieval extinction protocol daily for about two weeks, after which their memory was reinstated using acute drug injection (non-contingent upon nose poking). Xue and colleagues found that nose poking behaviour decreased only in rats that underwent extinction sessions 10 min post-retrieval. The authors also examined drug-related Pavlovian learning using conditioned place preference to a context associated with drug and found more robust results. This suggests that Pavlovian memories are rendered labile more readily than instrumental memories. A critical difference is that instrumental memories are usually stronger due to more intense training. Although several studies have shown that strong instrumental memories did not appear to undergo reconsolidation (e.g. Hernandez and Kelley 2004), a recent study found that introducing unexpectedness during the reminder session destabilizes a well-trained instrumental memory (Exton-McGuinness et al. 2015). Similar observation was shown for Pavlovian threat memories where targeting reconsolidation is difficult because of the strength of initial learning (Díaz-Mataix et al. 2013), consistent with the notion that some limitations of targeting reconsolidation may be overcome with variations in reactivation protocols.

The neural mechanisms mediating updating through post-retrieval extinction are still largely unknown (for reviews, see (Auber et al. 2013; Flavell et al. 2013). The working model emerging from studies thus far suggests that learning induces persistently potentiated synaptic strengthening in the lateral amygdala, by synaptic surface expression of calcium-impermeable AMPA receptors (CI-AMPAr), which are more stable at the synapse compared to the less stable calcium-permeable AMPA receptors (CP-AMPAr). Memory retrieval engages NMDA receptor-induced exchange of CI-AMPAr to CP-AMPAr. This process of

CI-AMPAR endocytosis followed by CP-AMPAR insertion causes an unstable state of synaptic potentiation. The newly inserted CP-AMPARs appear to contribute to memory updating following reactivation but are removed from the synapses over the course of post-retrieval extinction (Clem and Huganir 2010; Hong et al. 2013; Monfils et al. 2009; Tedesco et al. 2014). Further understanding of the neural mechanisms underlying the reactivation–extinction paradigm may help to optimize its effectiveness in human studies.

5.2 Reactivation–Extinction: Preclinical Human Studies

Evidence for reactivation–extinction effect was also demonstrated in humans using threat conditioning (Schiller et al. 2010). Three groups of participants learned to associate one out of two visual cues (CS+ and CS−) with an electric shock to the wrist. The index of threat was SCR. A day later, all groups underwent extinction training. One group had regular extinction with no reactivation of the memory. The two other groups were reminded of the CS prior to extinction, one group had extinction 10 min post-retrieval (during reconsolidation), and the other waited 6 h (after reconsolidation was presumably complete). The return of conditioned SCR was tested a day later. The groups that had no reminder–extinction or extinction 6 h after the reminder showed spontaneous recovery of the threat memory. Only the participants that underwent post-retrieval extinction after 10 min showed no evidence of threat memory. A follow-up session showed that the effect persisted about a year later.

The vast majority of post-retrieval extinction studies in animals were conducted by comparing between groups, as did the protocol above in humans, where only one simple threat association was studied. Real-life memories, however, are much more complex and likely include multiple memory traces. Schiller et al. (2010) also examined whether post-retrieval extinction would influence only the memory that was retrieved but not other memories formed during the same time and within the same context but were not reactivated. To study this, the participants learned to associate two out of three visual stimuli with shock. A day later, only one of the two CSs was reactivated, and 10 min later, all stimuli were presented repeatedly without the shock in an extinction session. A day later, the participants received 4 unsignaled shocks in order to reinstate the memory, and the test was conducted 10 min later by presenting the stimuli without the shock. The results showed that only the memory that was reactivated prior to extinction was not reinstated, suggesting that post-retrieval extinction is not only effective in humans but also specific to memories that return to a labile state upon retrieval.

The specificity of post-retrieval extinction is advantageous in preventing unwarranted memory modification, but it could also be a disadvantage if we wish to modify complex memories associated with traumatic events. To address this, Liu and colleagues (Liu et al. 2014) speculated that reactivating the memory using the US would modify all CSs associated with this US. The participants underwent threat conditioning where they learned to associate two visual stimuli with shock. A day later, the participants underwent US reactivation using a weaker shock, 10 min later underwent extinction training, and were tested a day later. Liu and colleagues found that US reactivation prevented the return of conditioned threat response to both CSs. They further showed that this effect persisted at

least 6 months and could also be achieved by extinguishing only one of the CSs. They also demonstrated similar results with memories that were two weeks old. These findings suggest that reactivating the central or 'binding' element of a memory might have a more overarching effect on reconsolidation. The clinical implication of this study is that re-exposure to a similar but milder adverse event might be beneficial under certain circumstances (see next section for a potential real-life demonstration of this effect).

Additional studies in humans demonstrated the post-retrieval extinction effect using a different modality of CS [auditory cue instead of visual; (Oyarzun et al. 2012)], as well as 7-day-old memories (Steinfurth et al. 2014), and in adolescents (Johnson and Casey 2015). Moreover, Agren et al. (2012b) suggested that individual differences in serotonin- and dopamine-related polymorphisms influenced post-retrieval extinction. Specifically, carriers of the short allele of the serotonin transporter length polymorphism (5-HTTLPR), and val allele homozygotes in the dopamine-related COMT Val158Met polymorphism showed enhanced reacquisition only if extinction training was performed outside, but not during, the reconsolidation window. In contrast, met allele and long-allele homozygotes did not show reacquisition regardless of reconsolidation conditions, suggesting that different allele carriers might have different reconsolidation windows. To fully assess genetic variations in reconsolidation, additional studies on sufficiently large populations are required.

Although several laboratories have reported that the reactivation–extinction paradigm persistently diminished the CR, other studies using different parameters were unable to find this effect, which might outline the boundary conditions of this phenomenon in humans (for reviews, see Agren 2014; Auber et al. 2013; Schiller and Phelps 2011). Some of these conditions include the use of CSs that were not initially neutral but rather innately frightful, such as images of spiders and snakes (Soeter and Kindt 2011). Threat conditioning to innately scary cues might induce stronger conditioning but could also engage a different neural mechanism altogether. Understanding the effect of fear-relevant stimuli might have important implications for anxiety disorders, which often involve memories that are both strong and innate, such as specific phobias (Mineka and Ohman 2002). Another important factor is the use of online expectancy ratings (Warren et al. 2014), as described in the previous paragraph. Again, it is possible that attention to the CS– US contingency during conditioning engages other neural mechanisms such as prefrontal circuits, which might diminish the impact of the reconsolidation processes within the amygdala on persistently attenuating threat responses.

Two recent studies (Agren et al. 2012a; Schiller et al. 2013) examined the neural mechanisms of the reactivation–extinction effect in the human brain using functional magnetic resonance imaging (fMRI). These studies suggest that reduction in conditioned threat responses following reactivation–extinction was coupled with reduction in amygdala reactivity to the CS (Agren et al. 2012a). Following extinction, the ventromedial prefrontal cortex (vmPFC) is thought to inhibit the amygdala and the expression of the CR enabling the expression of the extinction memory. Interestingly, unlike in standard extinction, with extinction during reconsolidation, less vmPFC involvement was detected. Furthermore, the amygdala and vmPFC were coactivated during standard extinction, but not when extinction occurred during reconsolidation (Schiller et al. 2013). These studies point to the possibility

that post-retrieval extinction might circumvent extinction-related pre-frontal processes, which might lead to threat memory updating within the amygdala.

5.3 Reactivation–Extinction: Studies in Clinical Populations

Persistently altering threat memories with the reactivation–extinction procedure is a promising avenue for noninvasive treatments of PTSD, but currently there are no published studies proactively examining the efficacy of a retrieval extinction approach in PTSD patients. A recent retroactive study (Weems and Graham 2014) might support the ecological validity of the reactivation–extinction paradigm in humans. This study examined the course of traumatic memories in youth from New Orleans that survived both hurricane Katrina in 2005 and hurricane Gustav in 2008. One month after hurricane Gustav, some participants recalled fewer negative memories of hurricane Katrina and had a reduction in PTSD symptoms induced by hurricane Katrina (Weems and Graham 2014). Those participants had a milder exposure to hurricane Gustav, which was significantly less devastating than hurricane Katrina. The authors found parallels between these observations and the reactivation–extinction paradigm. Exposure to hurricane Gustav may have served as a reminder for Katrina memories, similar to the US reactivation that Liu and colleagues used (described above; (Liu et al. 2014), and the experience of a milder storm may have led to the update of hurricane Katrina memories. The consequence of this sequence of events is reminiscent of the hypothesis that reactivation may serve as an update mechanism. However, this interpretation is speculative. Nevertheless, perhaps forms of treatment that mimic re-exposure to the trauma in a milder form (guided imagery, narrative rescripting, etc.) can capitalize on a reactivation update mechanism. The link between existing therapies and reconsolidation remains to be scientifically validated.

As outlined earlier, reconsolidation may also be harnessed to diminish maladaptive appetitive memories that underlie addiction. Drug-associated cues could trigger conditioned responses even after long periods of abstinence. The post-retrieval extinction procedure was recently adapted for drug addiction (Xue et al. 2012). In this study, inpatient detoxified heroin addicts underwent the following procedure: On Day 1, baseline measures of cue-induced heroin craving, including heart rate, blood pressure, and the visual analogue scale, were taken. On Days 2 and 3, the participants were divided into three groups: one group was reminded of the drug memory using a 5-min presentation of videotaped heroin cues. Ten minutes later, they underwent 1 h of extinction training comprised of four consecutive sessions of repeated exposures to three different heroin-related cues. The second group underwent a similar procedure but had a 6-h break following the reminder, and the third group had the 1-h extinction training without the reminder (they were shown 5 min of a neutral video). Change in craving compared to baseline level was assessed during Day 4, as well as approximately one month and six months later. The only group that showed significant attenuation in craving that persisted at least six months was the group had extinction training 10 min after the drug cue reminder. These findings are an encouraging first step towards implementing reconsolidation update mechanisms in drug addiction interventions and prevention of relapse and are the only clinical support of the reactivation–extinction paradigm to date.

5.4 Reactivation–Extinction: Conclusions

Taken together, the evidence from non-human animal and preclinical human studies indicates that the reactivation–extinction paradigm might be a promising avenue for the development of noninvasive techniques to modify threat- and drug-related memories. Again, the strength and age of memories as well as the type of memory may be limiting factors to flexibility. But animal and human studies suggest that the chance of inducing renewed flexibility at reactivation can be increased through specific pharmacological manipulations or by reactivating the binding element of a memory and introducing a degree of unexpectedness. The mnemonic mechanism through which the reactivation–extinction paradigm exerts its effects is not entirely clear. Modification via reconsolidation is one option, but reactivation could also allow more optimal integration between an old memory and new information through new learning. Initial neuroimaging evidence indicates that the reactivation– extinction paradigm does cause a substantial alteration of functioning within the brain network that supports threat and safety memory. Further understanding of these underlying neural mechanisms could aid optimization of the effectiveness of the paradigm. It remains to be seen whether post-retrieval extinction would prove effective in modifying real-life memories, which are typically older, stronger, and multifaceted. Yet, the first study in a clinical population provides validity to further develop the paradigm for clinical use.

6 Conclusion, Limitations, and Future Directions

Targeting reconsolidation holds great clinical promise as it allows the modification of specific memories and may prevent the return of learned responses and memories that contribute to maladaptive behaviour. Here, we have discussed translational efforts aimed at altering memories by targeting reconsolidation using biological treatments (electrical stimulation, noradrenergic antagonists) or behavioural interference (reactivation–extinction paradigm). Both approaches have been used successfully to modify aversive and appetitive memories in non-human animals, in healthy human subjects, and in clinical populations. Yet not all studies have been efficacious, and the exact mnemonic mechanisms that have been affected by the different studies are not always clear. Reconsolidation depends on de novo protein synthesis (Nader and Hardt 2009), and noradrenergic antagonists, or reactivation–extinction, are indirect effectors of protein synthesis at best. We are convinced that increasing understanding of the mechanism and limitations of memory flexibility upon reactivation can help optimize efficacy of treatments for psychiatric patients. This requires translational approaches from non-human animals, to healthy human subjects and clinical populations that take into account the translational limitations across species and study populations.

6.1 Limitations

Several limitations to memory flexibility at reactivation are becoming apparent. The dependency of memories on specific brain regions and their change over time with systems consolidation might limit the possibility to alter memories. It seems that both recent and remote memories that depend on the amygdala, such as arousal-related responses, can be altered upon reactivation. Operant behaviours that involve the striatum appear less flexible. Hippocampus-dependent memories such as contextual and episodic memories may become

less sensitive to reactivation-dependent flexibility as memories undergo systems consolidation and become to depend more on cortical regions. As maladaptive memories in patients are often old and hippocampus-dependent memories may play a more prominent role in humans than rodents, this could be an important limiting factor to translational efforts.

Further, the effectiveness of noradrenergic antagonists to affect reactivated episodic memories may be limited to eliminating the emotional enhancement effect that involves amygdala-dependent modulation of the hippocampus via a beta-adrenergic mechanism. At this point, it is unclear whether this is a limitation of flexibility of memory is due to intrinsic qualities of distinct brain regions, or the result of the mechanisms of action of propranolol, or a combination of both. As episodic memories contribute to the aetiology and maintenance of maladaptive behaviours in patients, it will be critical to develop methods that can overcome this limitation to translational approaches.

Not all memory retrievals result in memory reactivation and flexibility. Brief reminder exposures trigger reconsolidation, whereas longer or repeated exposures result in extinction, although this may depend on the initial learning circumstance (Eisenberg et al. 2003; Pedreira and Maldonado 2003; Suzuki et al. 2004). In addition, the reminder cue can determine which specific memory becomes flexible and which does not (Debiec et al. 2006; Muravieva and Alberini 2010; Schiller et al. 2010). More broad memory flexibility might be induced by reactivation of a ‘binding element’ (Liu et al. 2014), and flexibility may require the expression of a to-be-modified response at reactivation (Sevenster et al. 2012). The reactivation of a memory thus requires the reactivation cue to be similar to the learning situation. Yet several studies also suggest that there has to be some form of mismatch between the expectation and outcome at the time of reactivation for memory flexibility to be induced (Díaz-Mataix et al. 2013; Morris et al. 2006; Sevenster et al. 2013; 2014). Thus, the conditions of reactivation can determine whether memory becomes flexible and which specific behavioural responses can be modified. The identification of the reactivation conditions that lead to the most optimal treatment outcome for a specific patient will thus be critical to overcome limitations of memory flexibility.

Several interindividual differences may also be limiting factors to translational efficacy of approaches targeting memory flexibility. One report suggested that propranolol only had an effect on reactivated aversive memories in women (Miller et al. 2004). Sex may thus be a determining factor in memory flexibility, or this effect could be due to a difference in metabolic rate or dose sensitivity. Further, individual differences in genetics may be a limiting factor to memory flexibility (Agren et al. 2012b). Sex and genetics are important considerations for translational efforts considering that almost all studies in rodents are performed in males only and given that these animals are genetically nearly identical. Future studies in non-human animals will have to address these issues.

Learned maladaptive responses to innately dangerous stimuli or innately non-nocuous stimuli (e.g. arachnophobia versus anthophobia) may also affect the ability to modify reactivated memories. To date, this topic has not received much attention.

6.2 Future Directions

Future studies will have to address limiting factors to reactivation-dependent memory flexibility to develop more optimal translational approaches. Further, reconsolidation is not the only process that can be triggered at memory retrieval. Many studies have had difficulty meeting the critical criteria to demonstrate reconsolidation, especially in humans (for review, see Schiller and Phelps 2011). Not meeting the criteria to demonstrate reconsolidation leaves open the possibility of alternative explanations for memory alterations such as retrieval impairments, or new learning processes such as extinction or secondary encoding. It is important to realize that initial learning does not happen on a tabula rasa either. Memory is adaptive, and reconsolidation is one of several processes supporting memory flexibility (Kroes and Fernández 2012; McKenzie and Eichenbaum 2011). Critically assessing the mnemonic processes that support memory alterations following retrieval is imperative. Such understanding will allow developing control over these processes and developing the most effective strategies to yield optimal treatment outcomes for patients.

Here, we discussed noradrenergic antagonists as a pharmacological approach targeting reconsolidation. The development of other pharmacological approaches that are safe for use in humans may allow effectiveness to extend beyond arousal symptoms and emotional enhancement of explicit memory. Such developments include drugs targeting the cortisol-GR-BDNF system (Abrari et al. 2008; Chen et al. 2012; Pitman et al. 2011; Schwabe and Wolf 2010; Taubenfeld et al. 2009; Tronel and Alberini 2007) and might involve targeting neuron–glia interactions (Suzuki et al. 2011), methods to increase the chance of memory destabilization at reactivation using D-cycloserine (Lee et al. 2009; Wood et al. 2015) or HDAC inhibitors (Graff et al. 2014), or potentially even dietary interventions such as the use of curcumin (Monsey et al. 2015). Repeating memory reactivation and treatment over several sessions might also optimize clinical outcomes, but efficacy might be limited to a limited number of sessions (Brunet et al. 2011, 2014).

As we have discussed, treatments targeting reconsolidation seem most effective in altering amygdala-dependent learned responses reflecting hyperarousal. Maladaptive memories in psychiatric disorders are multifaceted, and beyond hyper-arousal symptoms include approach and avoidance behaviours and cognitive ruminations. Future research will have to develop translational approaches to target these behaviours as well. Finally, altering reactivated memories can contribute to the treatment of psychiatric disorders but is not a magical cure. Patients have often over many years adjusted their delay life to their disorder and can, for example, suffer from feelings such as guilt that are not solved by modifying memories. Yet altering reactivating memories holds the promise to contribute to more optimal treatment methods and help patients break the chains of maladaptive behaviours and work towards a healthier future.

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