

**MAKING LEAPS AND HITTING BOUNDARIES IN RECONSOLIDATION:
OVERCOMING BOUNDARY CONDITIONS TO INCREASE CLINICAL
TRANSLATABILITY OF RECONSOLIDATION-BASED THERAPIES**

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ABSTRACT

Reconsolidation results in the restabilisation, and thus persistence, of a memory made labile by retrieval, and interfering with this process is thought to enable modification or weakening of the original trace. As such, reconsolidation-blockade has been a focus of research aiming to target the maladaptive memories underlying mental health disorders, including post-traumatic stress disorder and drug addiction. Current first-line therapies are not effective for all patients, and a substantial proportion of those for whom therapies are effective later relapse. A reconsolidation-based intervention would be invaluable as an alternative treatment for these conditions. However, the translation of reconsolidation-based therapies to the clinic presents a number of challenges, with arguably the greatest being the overcoming of the boundary conditions governing the opening of the reconsolidation window. These include factors such as the age and strength of memory, and can broadly be divided into two categories: intrinsic features of the targeted memory itself, and parameters of the reactivation procedure used. With maladaptive memory characteristics inevitably varying amongst individuals, manipulation of the other limitations imposed by procedural variables have been explored to circumvent the boundary conditions on reconsolidation. Although several apparently discrepant results remain to be reconciled and these limitations yet to be truly defined, many studies have produced successful results which encouragingly demonstrate that boundary conditions may be overcome using various proposed strategies to enable translation of a reconsolidation-based intervention to clinical use.

KEYWORDS

Memory; mental health disorders; animal models; PTSD; addiction

INTRODUCTION

Reconsolidation is the process by which an existing memory, having entered a labile state following retrieval, is re-stabilised. Memory is now considered to be much more dynamic and malleable than previously thought, cycling through 'inactive' and 'active' states as it is retrieved and reconsolidated (Lewis 1979; Nader 2003). This reconceptualisation of memory followed early demonstrations of 'cue-dependent amnesia' (Misanin et al. 1968; Schneider and Sherman 1968), and became more widely accepted following the demonstration that a pavlovian auditory fear memory required protein synthesis to persist in the brain following a brief memory reminder or 'reactivation' session (Nader et al. 2000). Subsequently, reconsolidation has been observed across multiple species, from invertebrates to humans (see Haubrich and Nader 2016, for review). Although the initial consolidation and reconsolidation of memories share partially overlapping molecular mechanisms (see Tronson and Taylor 2007, for review), a key difference between consolidation and reconsolidation is the critical dependence of the latter on the *destabilisation* of memory. This is dissociable from memory *retrieval* (Milton et al. 2013; Rodriguez-Ortiz and Bermúdez-Rattoni 2017; Santoyo-Zedillo et al. 2014; Sevenster et al. 2012), and has been related to the concept of 'prediction error' and a 'mismatch' between what is expected, and what actually occurs, during the memory reactivation session (Pedreira et al. 2004). As such, reconsolidation is proposed to enable modification of existing memories so that they may be updated with new information and maintain relevance over time (Bermudez-Rattoni and McGaugh 2017; Dudai 2012; Lee 2009; Lee et al. 2017).

With the potential to modify and possibly weaken memories, manipulation of reconsolidation processes has been a focus in research aiming to develop new treatments for mental health disorders underpinned by the formation of maladaptive memories (Beckers and Kindt 2017; Dunbar and Taylor 2016; Elsey and Kindt 2017a; b; Kindt and van Emmerik 2016; Milton 2013; Milton and Everitt 2010; 2012; Taylor and Torregrossa 2015; Torregrossa and Taylor 2013). Post-traumatic stress disorder (PTSD) is one such condition, with aberrantly strong emotional memories resulting in the generalisation of trauma-related cues to safe contexts, and giving rise to symptoms of avoidance and intrusive re-experiencing of the trauma (American Psychiatric Association 2013). Conditions such as generalised anxiety disorder and phobias similarly involve fear-associated stimuli which trigger inappropriate/disproportionate aversive responses in safe contexts. Substance use disorders (SUDs) can also be conceptualised as disorders of maladaptive memory, with drug-associated stimuli maintaining drug-seeking and drug-taking behaviours and promoting relapse (Milton and Everitt 2010; 2012; Torregrossa et al. 2011; Tronson and Taylor 2013). A reconsolidation-based approach may therefore be able to interfere with avoidance or associative memories implicated in trauma- and anxiety-related disorders and substance use disorders. This interference of reconsolidation is generally either achieved by disrupting restabilisation of the

maladaptive memory pharmacologically, or by using behavioural techniques to attempt to overwrite, or rewrite, the maladaptive memory (see Walsh et al. 2018, for review).

Currently available therapies for mental health disorders are not efficacious for all patients (Holmes et al. 2014), and the development of reconsolidation-based therapies could therefore provide an important new treatment avenue. Exposure therapy is a first-line intervention which involves extinguishing the aversive response to the trauma-/anxiety-related stimulus (conditioned stimulus; CS) by extinction learning. However, for some patients it fails to produce any significant improvement, and of those successfully treated, a substantial proportion later relapse (Holmes et al. 2014). For patients for whom extinction-based approaches are unsuccessful, a reconsolidation interference alternative may offer hope, with studies showing that some memories resistant to extinction learning may be susceptible to reconsolidation-based interventions (Elsei and Kindt 2017a). Moreover, given that extinction learning creates a new inhibitory memory trace which competes with the original CS-fear memory, the potential for return of fear remains via renewal, reinstatement and spontaneous recovery (Bouton 2002). A reconsolidation-based approach, by contrast, would directly target the maladaptive memory and thus confer a key advantage over exposure therapy in preventing relapse.

Although the prospect of an alternative reconsolidation-based treatment seems promising, clinical translation is not without its challenges, even for ‘simple’ procedures such as fear conditioning (Haaker et al. 2019). Much of the research into reconsolidation has been conducted in animals, studying memories with relevance to mental health disorders. Although certainly useful in simplifying disorders to facilitate understanding, these animal studies do not, and were not designed to, fully capture the clinical context of psychiatric conditions (Rutherford and Milton 2022). For example, experimental studies in both animals and humans often involve experimentally generated memories reactivated only a few days or weeks after training, whereas the naturalistic memories underlying conditions such as PTSD and phobias are typically much older and stronger (Walsh et al. 2018). Notwithstanding the substantial evidence supporting reconsolidation interference as a viable means of targeting maladaptive memories, there have also been several apparent failures to replicate reconsolidation-based effects (Bos et al. 2014; Luyten and Beckers 2017; Luyten et al. 2021; Rotondo et al. 2022; Schroyens et al. 2017). These do not necessarily negate the potential of a reconsolidation-based approach, but certainly remain to be reconciled if it is to progress to clinical application. Unsuccessful findings are generally attributed to so-called ‘boundary conditions’, which determine whether a reconsolidation process occurs following memory reactivation. However, these boundary conditions are still yet to be defined, and hence present an ambiguous yet significant barrier for reconsolidation-based approaches on the path to clinical use. Here, we consider what is

known about these boundary conditions, and how they might be overcome to facilitate the translation of reconsolidation-based approaches to the clinic, beyond the relatively small-scale trials that have been conducted to date (Brunet et al. 2008; Brunet et al. 2011; Das et al. 2019; Hollandt and Richter 2022; Kindt and van Emmerik 2016; Lonergan et al. 2016; Soeter and Kindt 2015; Wood et al. 2015).

BOUNDARY CONDITIONS ON THE OCCURRENCE AND DISRUPTION OF RECONSOLIDATION

The reconsolidation window is the transient reactivation-induced period in which memory is destabilised and reconsolidation processes occur. This window may be opened by presentation of a reminder of the original training experience, for example with CS presentation by *in vivo* exposure or using virtual reality (Maples-Keller et al. 2017; van Gelderen et al. 2018). This window is thought to remain open for a few hours, with amnesic interventions no longer having an effect when administered six hours post-reactivation (Nader et al. 2000). However, the exact duration for which the memory remains labile is still unclear and appears to vary across experiments from different labs (Carneiro et al. 2022). Furthermore, retrieval does not equate to destabilisation, and so in some cases the reconsolidation window does not open at all. Following memory retrieval, whether and for how long the reconsolidation window opens is hypothesised to be governed by various boundary conditions. Broadly, these can be divided into two categories: characteristics of the memory itself, and parameters of the reactivation procedure.

Memory strength and age have been argued to present two major boundary conditions constraining initiation of reconsolidation, with stronger and older memories appearing more resistant to disruption (Milekic and Alberini 2002; Suzuki et al. 2004). The boundary conditions on reconsolidation were prominently demonstrated early in the new era of reconsolidation research, with Suzuki et al. (2004) showing that under conditions sufficient to disrupt the reconsolidation of a weak (1-shock) contextual fear memory, a strong (3-shock) memory remained unimpaired. Similarly, contextual fear memories that were 1 or 3 weeks old, but not 8 weeks old, were disrupted by the administration of the protein synthesis inhibitor anisomycin (Suzuki et al. 2004). One possible explanation for the observed effects of memory age is the 'lingering consolidation' hypothesis, which postulates that consolidation/reconsolidation may be a much more prolonged process than generally thought (Dudai and Eisenberg 2004). In the case of stronger memories, their resistance to disruption is suggested to perhaps be due to increased consolidation at encoding resulting in the memory being more widely represented in neural networks and thus more stable. It is likely these memory characteristics may be inherently related and interact in acting as boundary conditions on reconsolidation, with the passage of time offering opportunities for intermittent memory

reactivation and strengthening (Alberini 2011). However, rather than imposing an intrinsic limit on the destabilisation of memories, the strength and age of a memory may simply shift the boundary conditions governing memory destabilisation. Old and strong memories do undergo reconsolidation (Lee et al. 2005; Winters et al. 2009), though the relationship between memory strength and age, and associated boundary conditions, is not necessarily straightforward (Flavell and Lee 2013; Reichelt and Lee 2013).

Consistent with hypotheses that reconsolidation serves to update memories in order to maintain their relevance over time, studies show a certain degree of mismatch between what is expected based on the memory and what actually occurs at retrieval (prediction error; PE) is necessary for reconsolidation processes to occur. This was investigated parametrically both in humans (Sevenster et al. 2014) and rats (Merlo et al. 2014) that had undergone discrete pavlovian fear conditioning. In both species, the relationship between prediction error and the engagement of reconsolidation was not monotonic; rather, a brief re-exposure leads to the engagement of reconsolidation mechanisms, while prolonged re-exposure induces extinction. In rats, intermediate re-exposures have been shown to engage neither reconsolidation nor extinction (Merlo et al. 2014), with molecular markers of plasticity corroborating that neither process is engaged (Merlo et al. 2018). This ‘limbo’ or ‘null point’ has also been observed for contextual fear memories (Cassini et al. 2017) and appetitive memories (Flavell and Lee 2013; Reichelt and Lee 2013). Consequently, the degree of prediction error between the individual’s prior expectations and the reactivation session is a major boundary that demarcates whether memory reactivation results in simple retrieval, reconsolidation or new learning (Vaverková et al. 2020).

Another important factor governing the boundary conditions is the expectation of the individual, which will determine the extent to which a mismatch occurs between the sensory input received in the memory reactivation session, and what was expected on the basis of prior experience (Milton et al. 2023). This has been much less studied in the context of reconsolidation than prediction error (though see Gershman et al. 2017; Monfils and Holmes 2018) but is likely to be no less important. In one computational model of avoidance conditioning (Osan et al. 2011), simulations suggested reconsolidation interventions to be more effective where the reactivation context was first encountered in the initial conditioning event (Santiago and Tort 2020). It was revealed that having previous knowledge of the currently aversive context as safe influences the opening of reconsolidation and extinction windows — perhaps due to there being varying degrees of prediction error at reactivation when an individual has mixed aversive and safe memories of the context, compared to only aversive memories. Moreover, as aversive memories differ from appetitive memories, and pavlovian memories from instrumental memories, and so on, in the mechanisms and

brain areas that they recruit, distinct types of memory may show differential susceptibility to reconsolidation disruption. Most of the literature thus far has focused on aversive associative memories which, although are certainly crucial in disorders such as PTSD and phobia, are likely less important in SUDs than appetitive drug memories (conditioned withdrawal notwithstanding). In the particular case of addiction, habitual instrumental memories play a significant role in maintenance of drug-seeking and drug-taking behaviours. The boundary conditions for instrumental memories have been much less investigated than those for pavlovian memories, and where they have been studied, key differences appear to exist. For example, instrumental memories appear to require reinforcement at reactivation, but under different contingencies compared to initial training, in order to destabilise (Exton-McGuinness et al. 2019; Exton-McGuinness and Lee 2015; Exton-McGuinness et al. 2014).

In addition to the boundary conditions posed by features of the targeted memory and the conditions of retrieval, greater variation in the outcome of a reconsolidation procedure is introduced by inter-individual differences. This variability likely exists even within boundary conditions themselves, particularly as prior experience will vary between individuals (Kuijer et al. 2020; Santiago and Tort 2020). Even for pavlovian memories, where there is greater experimental control of the prior learning history, individual differences in the attribution of incentive value and attention to drug-associated cues during learning may influence the optimal reactivation parameters for each individual (Kuijer et al. 2020). As individuals seem to learn about associative cues differentially, it likely follows that whether a retrieval procedure results in memory updating via reconsolidation, or new learning via extinction, also varies accordingly. Although the focus of the paper was on the appetitive cues underlying addiction, it is possible that individual variation may similarly exist in attribution of emotional salience to aversive CSs, and consequently also affect procedure outcomes. Consistent with the proposed influence of differential learning, in studying the effects of reconsolidation update mechanisms on maladaptive reward memories in hazardous drinkers, Gale *et al.* (2021) found inter-individual variability in responsiveness to corrective learning which predicted subsequent responses to alcohol under certain conditions.

With numerous parameters to consider at the level of each individual, it may be questioned whether boundary conditions are too limiting for any realistic translation of reconsolidation-based approaches to clinical use. Most studies in the reconsolidation literature involve targeting of memories acquired in laboratory settings; in comparison to those underlying conditions such as PTSD, which may be decades old and as a result of great trauma, these experimentally induced memories are typically significantly younger and perhaps also much weaker. Considering increased resistance to reconsolidation has been observed with just a few weeks difference in memory age, and by giving

only two additional footshocks at training to vary memory strength (Suzuki et al. 2004), it is understandable that some may be doubtful that reconsolidation disruption could ever be a viable means of targeting clinically relevant maladaptive memories. Moreover, being a behaviourally silent process, and without any markers that can be used *in vivo* in real-time, it is currently not possible to determine whether memory destabilisation has occurred and thus the level of PE required in individual cases (see Milton et al. 2023, for review). Finally, consistent with the view that prior expectation will influence the boundary conditions for reconsolidation, in humans fear memories of different strengths appear to require different degrees of prediction error for destabilisation (Chen et al. 2021). However, in spite of all these hurdles, there have been some observations of reconsolidation interference in clinically relevant populations — for example, disrupting reconsolidation has been shown to attenuate expression of even lifelong fear memories in patients with spider phobia (Björkstrand et al. 2016; Soeter and Kindt 2015). With the investigation of boundary conditions, and how they might be overcome, being a focus of recent research, many studies have encouragingly shown that these limits are not absolute (Elsey and Kindt 2017a), and several strategies have been proposed which may enable a reconsolidation-based approach to be an effective means of targeting underlying maladaptive memories clinically.

CIRCUMVENTING BOUNDARY CONDITIONS TO OPEN THE RECONSOLIDATION WINDOW

To overcome boundary conditions produced by intrinsic memory characteristics such as strength and age, it may be possible to manipulate the parameters of reactivation to optimise intervention outcomes. For pharmacological reconsolidation-based interventions, increasing the dose of amnesic agent given may be one such way of achieving this. Although old fear memories appear seemingly resistant to the effects of the GABA_AR agonist midazolam given at a dose that disrupts recently acquired fear memories, they can be disrupted following administration of higher doses of the same drug (Bustos et al. 2009). This need for a greater amount of amnesic agent with age perhaps reflects the gradual distribution of the memory throughout brain regions, or possibly its reducing requirement for *de novo* protein synthesis following retrieval, as result of ‘lingering consolidation’ (Dudai and Eisenberg 2004) or otherwise. Despite observed successes, this strategy becomes self-limiting as increasing drug doses are generally associated with greater risk of adverse effects, restricting potential for clinical use.

Without such pharmacological implications, extending the duration of the reactivation session is another procedural change that can be made in attempt to circumvent boundary conditions. Extending the duration of the memory reactivation session (beyond that necessary to induce the destabilisation of recent fear memories) was effective to destabilise old contextual fear memories (Bustos et al.

2009; Suzuki et al. 2004). However, caution would need to be applied in using this approach with clinical populations, as with increasing re-exposure durations other mnemonic processes may be recruited which would prevent the occurrence of reconsolidation (Merlo et al. 2014), particularly as the relationship between memory strength, age and the prediction error required for destabilisation does not appear to be monotonic (Flavell and Lee 2013). Otherwise, there is much evidence supporting that greater reactivation session durations facilitate the induction of reconsolidation in more resistant memories. These effects may perhaps be conceptualised as being the result of longer re-exposure producing a sustained, and thus greater degree of, prediction error, which is itself a boundary condition on the opening of the reconsolidation window that may be manipulated (Gershman et al. 2017; Hu et al. 2018).

As it is proposed to delineate the transition to and beyond reconsolidation (Merlo et al. 2014; Sevenster et al. 2014), adjusting the level of prediction error at reactivation may enable the destabilisation of seemingly reconsolidation-resistant memories. Object recognition memories (which, unlike pavlovian conditioning, is not compromised by potential extinction-related interpretations), can be destabilised despite their age and strength with the incorporation of additional novel stimuli during the memory reactivation session (Winters et al. 2009). Compared to younger and weaker memories which were disrupted regardless of conditions at retrieval, as memories increased in age (time between sample and reactivation phases) and strength (sample object exploration), the effects of MK-801 (NMDAR antagonist) were abolished unless salient novel contextual information was present during reactivation. Comparable results can be observed with fear memories (Chen et al. 2021), although it appears that verbal instructions alone are insufficient to enhance prediction error (Marinos et al. 2022). Altogether, these findings suggest that where reconsolidation appears to be hindered by limits imposed by memory age and strength, varying the degree of PE at reactivation may allow these boundaries to be overcome.

One potential account for the requirement of increased prediction error to induce the destabilisation of old and strong memories is that the increased re-exposure may sufficiently enhance CS intensity/salience at retrieval to exceed putative thresholds on induction of plasticity changes that mediate boundary conditions and whether a memory is destabilised (Zhang et al. 2018). With GluN2B-containing NMDA receptors shown to be necessary for memory destabilisation (Ben Mamou et al. 2006; Milton et al. 2013), it is possible that metaplastic increases in the ratio of GluN2A-containing to GluN2B-containing NMDA receptors contribute to memory stability that confers resistance to reconsolidation (Holehonnur et al. 2016; Zhang et al. 2018). Signalled by changes in dopamine activity, greater degrees of prediction error may thus enable destabilisation of more resistant memories by resulting in sufficient changes in NMDAR activation.

Understanding the neurotransmitter systems necessary to induce memory destabilisation may allow identification of pharmacological agents that may facilitate the labilisation of older and stronger memories and thus the induction of reconsolidation. Differential pharmacological modulation of the relative activation of NMDAR subunits may be one potential means of achieving this. If the downregulation of GluN2B-containing NMDARs mediates the resistance to destabilisation seen with older and stronger memories (Zhang et al. 2018), there may be potential for use of NMDAR subunit-selective pharmacological agents in overcoming the effects of boundary conditions on reconsolidation. Consistent with this hypothesised role of NMDAR in memory destabilisation and reconsolidation, administration of the NMDAR partial agonist D-cycloserine (DCS) can unmask the reconsolidation-disruptive effects of the α_2 -adrenoceptor agonist clonidine and cannabidiol on strong PTSD-like memories (Gazarini et al. 2014). Using DCS in a dual step pharmacological intervention, clonidine and cannabidiol became able to produce significantly less freezing in rats with enhanced memories produced by post-conditioning yohimbine, and also attenuate observed fear generalisation. While pharmacological agents certainly show much potential in attenuating the effects of boundary conditions and promoting memory destabilisation, there are always reservations with taking approaches involving administration of additional drugs. In addition to general risk of adverse effects and toxicity, considerations must also be made in terms of differential responding of individuals to pharmacological agents and potential drug interactions (with other prescribed drugs and/or agents used to disrupt reconsolidation). Furthermore, care would need to be taken not to engage extinction mechanisms, as DCS can facilitate the consolidation of extinction memories (Lee et al. 2006; Merlo et al. 2014).

Considering the risks of adverse effects with pharmacological approaches, a behavioural intervention may be a more feasible means of overcoming boundary conditions in patients. Campbell *et al.* (2021) investigated whether an extinction-renewal procedure may attenuate behavioural expression of strong memories to facilitate the induction of subsequent destabilisation and reconsolidation. Following overtraining and the generation of a strong fear memory, extinction of the fear-conditioned CS over 8 days prior to the reactivation procedure rendered the memory once again susceptible to disruption with midazolam. This suggests that reducing the behavioural expression of a strong fear memory, via extinction, can render it susceptible to reconsolidation disruption.

Despite it being a relatively recent area of research, several potential strategies have been proposed for circumventing the boundary conditions that can render maladaptive memories underlying various psychiatric disorders resistant to reconsolidation. These approaches are not without their disadvantages and currently require more supporting evidence before use in treatment, but certainly

demonstrate that the challenge presented by limiting memory features for the clinical translation of a reconsolidation-based approach is one worth tackling. Although they have generally been studied in isolation, the potential for the utility of these interventions may be further increased by using different strategies in conjunction with one another. One possibility is that this may produce a summative effect in promoting memory destabilisation and enabling reconsolidation disruption of particularly resilient memories. For example, the greater doses of amnestic agents required to disrupt old and strong memories (Bustos et al. 2009) could potentially be reduced by combining this approach with prior extinction training (Campbell et al. 2021). Therefore, along with investigating the effects of these proposed strategies in clinical populations, there may also be merit in exploring how different interventions may be used in combinatorial fashion to overcome the boundary conditions and issues currently limiting the translation of reconsolidation-based approaches to clinical use.

RETRIEVAL EXTINCTION: A CASE STUDY ON THE EFFECTS OF BOUNDARY CONDITIONS

Extinction within the reconsolidation window, or ‘retrieval-extinction’, consists of extinction training following a memory reactivation session, when the lability window should be open (Monfils et al. 2009). It has been suggested that, when applied during the reconsolidation window, extinction learning may be able to result in lasting revaluation of the CS as safe, leading to weakening of the storage or retrieval of the fear memory (Monfils et al. 2009), although this is not the only potential explanation for the persistently reduced spontaneous recovery, reinstatement and renewal observed after this procedure (Cahill and Milton 2019).

Following the seminal work of Monfils et al. (2009), numerous studies have applied the retrieval-extinction procedure across different types of memories and species, including humans (Agren 2014; Hollandt and Richter 2022; Lee et al. 2017; Maples-Keller et al. 2017; Phelps and Hofmann 2019; Schiller et al. 2010; Vermes et al. 2020). In a clinical population of heroin-addicted patients trying to maintain abstinence, a modified retrieval-extinction procedure attenuated cue-induced drug craving, with effects lasting up to 180 days (Xue et al. 2012). Similar results were reported for patients addicted to nicotine, where retrieval-extinction substantially reduced craving to both familiar and novel smoking cues, and also decreased the average number of cigarettes smoked per day for one month after treatment with *in vivo* exposure (Germeroth et al. 2017) and virtual reality exposure (Zandonai et al. 2021). With a clinical sample of active smokers, these results encouragingly highlight a possibility for particularly strong and old memories (resulting from extensive cue-drug pairings over many years) to be susceptible to memory updating interventions, as well as a potential

advantage of retrieval-extinction over extinction-based interventions in preventing reinstatement via generalisability of its effects to related cues.

However, studies of retrieval-extinction have not all been successful, with mixed findings throughout the literature (see Ecker 2022 for review). In a meta-analysis of relevant papers, it was suggested that the retrieval-extinction procedure was no more effective than standard extinction for fear memories in animals, and produced only a small-to-moderate effect for human fear memories (Kredlow et al. 2016). More recently, a direct, highly-powered replication of the retrieval-extinction procedure for fear memories in humans found no differences between the retrieval-extinction and standard extinction manipulations (Chalkia et al. 2020). Along with other replication failures, these findings may give cause to doubt whether there is adequate evidence in the literature that retrieval-extinction can prevent the return of fear in humans (Chalkia et al. 2020). However, it should be noted that with the levels of power reported for many reconsolidation experiments, it would be anticipated that approximately one third of studies would fail to replicate reconsolidation-based effects (Carneiro et al. 2022).

Considering there have still been a substantial number of successful findings (Agren et al. 2012; Chen et al. 2021; Dural et al. 2022; Hollandt and Richter 2022; Hu et al. 2018; Junjiao et al. 2019; Li et al. 2017; Liu et al. 2014; Oyarzún et al. 2012; Schiller et al. 2010), some hypothesise that observed replication failures may be attributed to boundary conditions narrowing the window within which retrieval-extinction is effective (Zuccolo and Hunziker 2019). If it does indeed operate via a reconsolidation updating mechanism, retrieval-extinction would also be susceptible to any interindividual differences affecting reconsolidation, including those in boundary conditions themselves (Kuijjer et al. 2020). Since it also consists of an extinction component, the success of retrieval-extinction may additionally be influenced by individual variation in extinction learning. These differences may be in individual learning rates, attention to and engagement with CSs during the reactivation trial, and even in the stress state of the individual at the time (Kuijjer et al. 2020). Further inter-individual variation in conditioning and extinction outcomes has also been proposed to arise from numerous biological and experiential variables — including age, sex, hormone levels, brain morphology and even contraceptive use — and their interactions (Lonsdorf and Merz 2017). With the mechanism of retrieval-extinction yet to be fully understood, it may be that these factors determine whether reconsolidation or extinction processes are engaged in a certain individual under given conditions. Although perhaps not successful in all individuals, retrieval-extinction appears to have potential to produce great benefit for some patients. As such, it would be worthwhile to identify those for whom a retrieval-extinction intervention may be effective and extend this population by refining the procedure to overcome the limits imposed by boundary conditions.

CONCLUSION

A key challenge hindering the translation of reconsolidation-based approaches into the clinic takes the form of unspecified boundary conditions. In addition to more general restrictions, such as the requirement of prediction error and the opening of the reconsolidation window lasting less than six hours, there are also numerous limits imposed by significant variation at the level of the individual. These individual differences influencing occurrence of reconsolidation can be found in features of the targeted memory (such as memory strength and age), in individual qualities (such as learning rates), and in individual states (e.g. stress levels at the time of treatment). These boundary conditions have also been found to interact with one another, giving rise to even greater potential for variability in the outcomes of reconsolidation-based interventions. For almost two decades, boundary conditions have presented a challenge to reconsolidation research, and their persistence as a barrier over the years appears to be rooted in the core problem that memory destabilisation cannot be measured online and *in vivo*, but rather needs to be inferred *post hoc* by the effects of a reconsolidation-based intervention (Milton et al. 2023).

In increasing the potential for clinical translation of reconsolidation-based approaches, a means of selecting the appropriate parameters for individual cases must be delineated to optimise intervention outcomes. As different patients will vary in their prior susceptibility to developing psychiatric disorders, in the severity of their symptoms, and in the characteristics of the underlying maladaptive memories, the same procedural conditions will unlikely be effective for all patients — as is the case even for current first-line interventions (including exposure therapy). The translation of reconsolidation interventions to clinical use thus necessitates precise specification, and perhaps even quantification, of the parameters governing the opening of the reconsolidation window and the interactions between them in exerting their influences. To achieve this, both further experimental research and deeper analysis of previous inconsistent and contradictory findings would be required. Not only would this help maximise treatment efficacy, but it would also importantly ensure that any reconsolidation disruption intervention is used safely, considering there is a risk that memory reactivation can result in extinction learning in lieu of reconsolidation and that this extinction memory may be affected instead. To facilitate both research and increase clinical translatability further, the development of neural markers of memory destabilisation and restabilisation that can be used *in vivo* in real-time would be extremely valuable. In experimental studies, susceptibility to amnesic agents has been a commonly used indicator of the occurrence of reconsolidation but this is only an indirect measurement, and thus development of such markers would reduce ambiguity in the interpretation of results. Furthermore, especially as it cannot be measured directly, it would be useful in determining the degree of prediction error sufficient for the destabilisation of targeted

memories in different individuals, perhaps using electroencephalography or pupillometry markers (Preuschoff et al. 2011).

Currently available treatments are effective for many patients but not yet for all, and a substantial proportion of those for which it was successful later go on to relapse, and thus there remains a need to develop alternative treatments. A reconsolidation-based approach has great promise in becoming one such alternative treatment and also potentially offers the option of using pharmacological agents or behavioural procedures to bring about its effects, allowing for flexibility in the treatment of patients according to individual characteristics and preferences. As reconsolidation disruption would require only a single, short phase of therapy, it could be relatively easily implemented with minimal clinician/patient burden and potentially even incorporated into treatment programmes to act synergistically with other therapeutic components. Particularly for a non-pharmacological reconsolidation interference procedure such as retrieval-extinction, only the addition of a memory reactivation trial to widely used exposure therapy procedures may be required to produce significant effects. The prospect of taking a reconsolidation-based approach to treat conditions such as PTSD and SUDs is particularly promising as, in interfering with the original memory directly, effects may be more persistent and patients less susceptible to relapse. As such, if boundary conditions were to be operationalised and the proposed strategies to overcome them refined, reconsolidation-based interventions show much potential in having significant clinical impact in the treatment of psychiatric disorders with underlying maladaptive memories.

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