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Abstract

The observation that pharmacological treatment at, or shortly after, the reactivation of a memory leads to subsequent long-lasting amnesia or memory strengthening is held to be a defining feature of memory reconsolidation. The bidirectional nature of synaptic plasticity modulation logically predicts memory updating as a normal part of memory processing. Accordingly, many have suggested that the retrieval-induced plasticity is ideally placed to enable memories to be updated with new information. This hypothesis has been tested experimentally, with a translational perspective, by attempts to update potentially maladaptive memories in order to reduce their problematic impact. Here, we review the progress on such reconsolidation-update studies, highlighting their translational exploitation and addressing recent challenges to the reconsolidation field.

Reconsolidation and the dynamic nature of memory

The retrieval and expression of an existing memory can lead to memory lability. What this means is that the reactivated memory becomes vulnerable to the effects of a number of different interventions. Canonically, these interventions have been pharmacological in nature, but in recent years, the scope of intervention has broadened into non-pharmacological (i.e. behavioral) treatments. The effect of these interventions to impair subsequent memory expression, and the phenomenological similarity to the effects of post-learning treatment, has led to their interpretation within a memory reconsolidation framework (See Glossary).

Three lines of evidence support the existence of a stabilization period on the order of hours after the acquisition of new memories. First, performance can be impaired if amnesic treatments such as electroconvulsive shock [1] or protein synthesis inhibitors [2] are given after learning. Second, performance can be impaired if new competing learning occurs after the initial learning [3]. Third, retention can be enhanced by administration of various compounds after the initial learning, such as strychnine [4]. Critically, all three manipulations are effective only when given soon after new learning and not when given after a delay. These findings gave rise to theories of synaptic consolidation [5, 6].

The same three lines of evidence point towards the existence of a post-retrieval restabilization period. First, performance can be impaired if a range of amnesic treatments are given after memory reactivation [7-11]. Second, performance can be impaired if new competing learning occurs after the reactivation [12, 13]. Third, retention can be enhanced by administration of various compounds after reactivation [14, 15]. Critically, again all three manipulations are effective only when given soon after reactivation but not when given after a delay. Ultimately, these findings led to the concept of a post-retrieval reconsolidation process [16-18]. That is, memory retrieval can lead to the destabilization of the memory, thereby necessitating a reconsolidation process to restabilize it.

The existence of a reconsolidation process begs the question of what, if any, function it serves. Many have suggested that the retrieval-induced plasticity is ideally placed to enable memories to be updated with new information [19-23]. This hypothesis has been tested experimentally, with a translational perspective, by attempts to update potentially maladaptive memories in order to reduce their problematic impact. Here, we will review the progress on such reconsolidation-update studies, highlighting their translational exploitation and addressing recent challenges to the reconsolidation field.

Reconsolidation updates memories

The observation that pharmacological treatment at, or shortly after, the reactivation of a memory leads to subsequent long-lasting amnesia is held to be a defining feature of memory reconsolidation [23, 24]. That is, memory reactivation can, but does not always [22, 25], result in the destabilization of the existing memory, thereby necessitating a protein synthesis-dependent phase of reconsolidation [26]. The bidirectional nature of synaptic plasticity modulation allows reactivated memories to be potentiated by pharmacological enhancement of neurochemical or cellular processes [15, 27]. Given the slim chance of encountering any of these laboratory amnesic agents in real life, these protocols indicate the existence of reconsolidation but not its functional role. If reconsolidation were to serve an adaptive function, there should be naturally occurring reconsolidation interference. A prominent working hypothesis is that reconsolidation enables the update of memories in order to maintain their relevance in the face of changing circumstances [22, 24, 28-31]. By extension, non-pharmacological interventions should have the ability to modify memory by influencing the reconsolidation process.

Behavioral interference protocols have the same structure as pharmacological protocols: Long-term memory is reactivated and behavioral interference (rather than administration of a pharmacological agent) ensues during the reconsolidation window. Just as pharmacological agents block or potentiate reconsolidation, behavioral interventions may similarly cause amnesia or strengthen the memory. Behavioral intervention, however, is uniquely poised to capitalize on reconsolidation in a constructive manner, allowing the incorporation of new information into an existing memory (Figure 1). The result of this update could be manifested in different forms, depending on the target memory system (Table 1). In procedural memories, for example, when a finger-tapping sequence memory was reactivated and followed by a new sequence, the accuracy of the initial memory diminished [13]. Declarative memories are also vulnerable to new or conflicting information that follows reactivation, affecting the amount of information retrieved from the original memory or enhancing intrusions of the new material into it [32]. For example, learning of a new list of objects following the reactivation of a previously learned list, caused items from the second learning to infiltrate the memory of the first list [33]. By the same token, when targeting emotional memories, extinction learning following reactivation of a threat-conditioned stimulus, may lead to long-term reduction in conditioned defensive responses [34, 35]. In all of these cases, the initial memory is not "erased" but rather incorporates new information, consistent with the view of reconsolidation updating.

The bidirectional nature of reconsolidation updating is especially relevant for emotion-related psychiatric disorders as it allows the modification of emotional memories in different directions. Neutral context memory can acquire threatening properties when reconsolidation mediates the incorporation of new threat learning experience [36];

contextual threat memories can strengthen with additional learning after retrieval in a process depending selectively on reconsolidation mechanisms [37]; and appetitive associative memories can lose their rewarding properties using the reactivation-extinction procedure [38, 39]. Another updating process that has effectively reduced reward-related responding involves reactivation followed by counterconditioning [40-42], where the appetitive conditioned stimulus is paired with an aversive outcome during reconsolidation.

Beyond integrating new information, behavioral intervention may also affect reconsolidation by engaging a cognitive process that competes for the same neural resources on which reconsolidation rely upon. A recent study [43] found that playing the computer game *Tetris* following reactivation of a trauma film memory reduced intrusive memories. Memory reactivation alone or playing *Tetris* without reactivation, did not affect the number of intrusions. Since *Tetris* is a visuospatial task, playing *Tetris* possibly competes with reconsolidation for memory-related neural resources and therefore interferes with the re-storage of the trauma film memory. Unlike the effects of pharmacological amnesic agents, however, this behavioral manipulation did not abolish subsequent retrievals (as in "erasure"), but rather affected only involuntary retrievals (the 'intrusions'). Better understanding the *Tetris* interference requires additional research assessing non-affective tasks that engage other neural resources thus gouging the degree of resource competition and hedonic impact.

These studies suggest that reconsolidation updating may be a viable pathway for non-invasively modifying maladaptive memories that are at the core of some psychiatric conditions. In the next section we describe the current state of psychiatric translation and possible paths for moving forward.

Translation of memory reconsolidation updating

To date, very little research in clinical populations has attempted testing and translating the reconsolidation-updating phenomenon for clinical treatment. The first study to harness the reactivation-extinction procedure was tested in addicted individuals [39]. The study included inpatient detoxified heroin-addicts that underwent a three-day procedure. One group of participants was reminded of the drug memory using a short video clip of heroin cues and then underwent extinction training (repeated exposures to heroin-related cues); another group went through a similar protocol but had a 6-hour break after the reminder; and the third group had extinction training without the reminder. The results show that only the first group showed significant attenuation in craving that persisted at least 6 months. These findings point to the potential efficacy of reconsolidation update mechanisms in drug addiction interventions and prevention of relapse.

Another attempt at manipulating maladaptive addiction-related memories using the reactivation-extinction procedure examined active cigarette smokers [44]. The participants

viewed a 5-minute video showing people smoking cigarettes to reactivate the relevant smoking-related memoires. Ten minutes later, the participants underwent extinction using extended exposure to smoking cues. Compared to a control group who had not undergone reactivation, the participants in the retrieval-extinction group showed rapid and lasting reduction in smoking frequency, as well as larger and enduring decrease in cue-induced craving that generalized to novel smoking cues. The relatively short follow up (1 month) and possibly insufficient statistical power to observe a full range of smoking outcomes (e.g., cotinine level, days abstinent, and relapse milestones) and are limitations to the nevertheless encouraging demonstration of the retrieval-extinction in another clinical population.

Taking a potentially more robust approach, a recent study used reactivation followed by counterconditioning in hazardous alcoholic drinkers [40]. The study induced memory reactivation using an actual alcoholic drink as the reminder, which the participants were almost allowed to drink but stopped. In two other control conditions, the participants got either a non-alcoholic beverage or an alcoholic beverage that they were allowed to consume. The premise of this manipulation is that prediction error at the time of retrieval (in this case violating expectation of alcohol consumption) is effective and even essential for successful memory destabilization [45-48]. Counterconditioning ensued 10 minutes following reactivation and included pairing of alcohol-related cues and disgusting images. The authors found retrieval-induced reduction of attentional bias, cue-induced craving, and liking ratings. A different manipulation for reconsolidation updating in a similar population of hazardous drinkers was less effective [49]. Here, the study used an emotion regulation technique of cognitive reappraisal following reactivation, but only verbal fluency for positively valenced alcohol-related words diminished when reappraisal followed memory reactivation. This effect was observed only when the reminder that consisted of omission-prediction error (preventing from drinking) but not value-prediction error (drink is unexpectedly bitter), pointing to specificity in the type of violation required for memory destabilization.

In anxiety and threat-related disorders, there is some promising but very preliminary support in implementing reconsolidation update mechanisms. Existing therapeutic interventions appear to engage reconsolidation mechanisms, but direct scientific evidence is lacking. For example, in a pilot study [50], individuals diagnosed with PTSD underwent a procedure termed, the reconsolidation of traumatic memories (RTM) protocol, which is a visual-kinesthetic protocol, also known as the rewind technique [51]. In brief, the procedure consists of a trauma reminder evoked by the patient retelling the trauma narrative, the patient is then reoriented to the present and imagines a movie theatre where the trauma memory is envisioned in black and white, from various vantage points, and so forth. The study reports a relatively strong effect where a majority of treated patients no longer met diagnostic criteria of PTSD. In order to directly link the critical

features of such protocols with reconsolidation, a fully controlled randomized experimental design ought to be employed.

Within the realm of anxiety disorders, three different studies targeted spider-phobia using the retrieval-extinction protocol. One study found no superiority of memory reactivation compared to no-reactivation, as both groups showed significant reduction in phobic symptoms, leaving open the possibility that retrieval-induced updating may augment treatment efficacy [52]. Another study found significant improvement following reactivation-extinction compared to the reversed (extinction-reactivation) procedure, but also found the unexpected immediate effect of rapid fear attenuation during exposure [53], providing some proof-of-concept Lastly, a study in a similar spider-phobic population [54], compared groups that saw a spider image either 10 minutes or 6 hours (within or outside the reconsolidation window, respectively) before undergoing an extinction session. The study found retrieval-induced enhancement in approach behavior toward the spiders in the 10-minute compared to the 6-hour group, an effect that lasted 6 months [55]. Together, these studies indicate that post-retrieval exposure to spider stimuli may effectively reduce spider phobia via reconsolidaion updating but protocol optimization is required.

An indirect evidence comes from a recent retroactive study [56] supporting the ecological validity of the reactivation-extinction paradigm. The study reviewed the course of traumatic memories in youth from New Orleans that survived both hurricane Katrina in 2005 and hurricane Gustav in 2008. Participants that had a milder exposure to hurricane Gustav, which was evidently less devastating than hurricane Katrina, recalled fewer negative memories of hurricane Katrina one month after hurricane Gustav, and showed lower levels of PTSD symptoms induced by hurricane Katrina [56]. There may be parallels between these observations and the reactivation-extinction paradigm. The milder exposure to hurricane Gustav may have acted as a reminder for Katrina memories. This form of reactivation resembles the use of an unconditioned stimulus as a reminder, such as a milder shock reminder of threat conditioning [57], a nicotine reminder in nicotine seeking rats and humans [58], and a cocaine reminder in cocaine seeking rats [59]. This form of reactivation may suffer fewer limitations as compared to the stimulus-specificity of reconsolidation impairments with cue exposure, it may also more effectively destabilize the memory due to its potency or the unexpected presentation parted from the conditioned cues [60]. By the same token, the experience of a milder storm may both generate sufficient prediction error to trigger destabilisation, and provide the updating experience to diminish the memory of hurricane Katrina. Thus, forms of treatment that resemble re-exposure to the trauma, albeit in a milder form (such as guided imagery), may capitalize on a reconsolidation update mechanism. These few studies provide very preliminary evidence for the potential therapeutic efficacy of reconsolidation updating. It is possible that existing therapies or even naturally occurring sequence of events may already

implement reconsolidation update processes. A direct link between treatment protocols and their underlying mechanisms ought to be scientifically validated.

The memory-updating role of reconsolidation is consistent with the manifestation of abnormally strong memories related to anxiety, trauma and addiction, which take over behavior and cripple adaptive function. On the one hand, recurrent retrieval of memories imbued with exceptionally strong emotion may effectively destabilize, strengthen and update these memories with added emotional impact. On the other hand, it is possible that due to conditions at the time of formation, these memories might lack destabilization mechanisms, impeding reconsolidation and therefore update-resistant. Note that these two conflicting scenarios – the "snow ball" effect of continuous strengthening or a "snap-shot" of the original event – result in the same phenotypic expression of an exceptionally strong emotional memory, but require opposite treatment. An overly reconsolidated memory would require reconsolidation interference, and destabilization-resistant memory would be insensitive to reconsolidation blockers and require destabilization promoters. These opposing scenarios are not mutually exclusive within the psychiatric realm as each may explain a different dimension of symptoms or individual variability within symptom domain. It may also explain why some treatments work while others are ineffective. Failure to dissociate these two aspects of memory updating may be at the heart of two main hurdles for translation: replication failure and treatment failure. It is therefore imperative to develop positive markers of memory destabilization and restabilization rather than indirectly assume these processes took place based on purely behavioral indices. In the next section, we identify and justify specific research questions addressing these obstacles that may have the greatest impact upon clinical translation.

The theoretical challenges of reactivation-dependent lability

The appeal of the reconsolidation-based interpretation of reactivation-dependent amnesia is that it implies a robust and long-lasting disruption/updating of the memory, providing the theoretical basis for a persistently beneficial therapeutic strategy for memory-based psychiatric disorders. However, memory reconsolidation is by no means a universally-accepted process; there having been a line of challenges to reconsolidation theory [Box 1]. Recently, alternative interpretations of reactivation-dependent amnesia have been (re)proposed. For example, amnesia might result from a state-dependent learning process [61, 62] or may simply be a form of uninhibited memory extinction [63]. State-dependent amnesia suggests that the amnestic drug treatment creates an altered internal physiological state, which becomes critical for future memory retrieval. Thus reinstatement of the internal physiological state can be sufficient to recover the impaired memory, as has been demonstrated for the effects of cycloheximide and lithium chloride on inhibitory avoidance and conditioned taste aversion memories [62]. The idea of reactivation-dependent amnesia resulting from uninhibited extinction similarly takes, as a fundamental

starting point, observation of recovery from amnesia [63]. Here, a weak reminder footshock delivered during contextual fear memory testing recovered subsequent contextual fear. This external reinstatement of the memory is perhaps less likely to be mediated by reinstatement of an internal physiological state, leading to the suggestion that reactivation-dependent amnesia is qualitatively similar to extinction, the latter being well-established to result in easily recoverable memory.

Focussing on reconsolidation-updating interventions, it is not clear if and how non-reconsolidation accounts can provide explanations for the induced amnesia. It may be possible that behavioural treatment can alter neural activity in a manner that creates a state-dependent effect. Similarly, behavioural intervention may somehow reduce the endogenous inhibition of extinction for associative memories. However, neither of these alternative accounts can explain the variety of interventions that have been demonstrated to show beneficial effects: retrieval-extinction, updating with counter-conditioning and competition for neural resources. Perhaps the only viable alternative to a reconsolidation-based explanation is specifically related to the original retrieval-extinction demonstration [34, 35], in that it is difficult to disambiguate between reconsolidation update and an enhancement of extinction. Pharmacological potentiation of extinction has been shown previously not only to result in a quantitative enhancement in the reduction of fear, but also a qualitative reduction in the propensity of fear to recover [64-66], thereby mirroring the persistent memory impairments characteristic of reconsolidation impairments and updates. Therefore, it is possible that the combination of retrieval with extinction training shortly after reduces fear not by updating the memory through the retrieval episode, but by the retrieval somehow priming or enhancing the subsequent extinction training. Such alternative interpretations of behaviourally-induced memory reduction are also pertinent to the observation that a reversal of the order of retrieval and extinction (i.e. extinction followed shortly afterwards by brief retrieval) can reduce alcohol seeking to a quantitatively similar level as retrieval-extinction [67]. While the reversed order is less consistent with a reconsolidation-based updating process, we would argue that it is not a logical extension to conclude that retrieval-extinction similarly does not exploit the reconsolidation process behaviorally.

Returning to the concept of potentiated extinction, although such an account of reconsolidation-update is plausible based upon the behavioral data alone, it may be less consistent with the outcomes of further exploration of the retrieval-extinction phenomenon. First, a parametric study in rats showed that retrieval-extinction only occurs under retrieval conditions that promote memory destabilization [68]. More convincingly, retrieval-extinction does not result in an enhancement of the neural mechanisms of extinction, but rather appears to diminish extinction-related prefrontal cortical activity [69]. Therefore, the updating of a destabilized memory trace is the most parsimonious interpretation of retrieval-extinction and other behavioral interventions.

While non-reconsolidation accounts of amnesia are unable to refute the existence of reconsolidation as a memory process, or to explain all of the hundreds of studies demonstrating reconsolidation, it remains possible that some observations of amnesia are attributable to non-reconsolidation mechanisms. Moreover, the theoretical basis of reactivation-dependent amnesia is unimportant from a clinical perspective. Whether or not the suppression of maladaptive memory expression is a result of impaired or updated memory reconsolidation, unleashed memory extinction or state-dependent inhibition of memory retrieval is immaterial as long as the suppression is robust and long lasting. Therefore, the central observations of memory recovery (i.e. only short-lasting memory impairment) that triggered the alternative explanations remain important and may be instead viewed constructively for future translation. In particular, translational studies will need to test explicitly for resilience against recovery procedures for both pharmacological and behavioral treatments. This is because it may be difficult to determine *a priori* whether any beneficial effects are truly a result of reconsolidation impairments/updates, and hence are likely to be persistent, or whether the treatment instead reduces maladaptive memory expression by non-reconsolidation means, with the possibility of recovery. At the clinical translational level, follow-up tests for psychiatric symptoms already implicitly test for resilience against everyday triggers of relapse. However, rarely do they explicitly quantify exposure to relapse-provoking situations, or directly compare the consequences of different interventions over long time periods. Moreover, there is a lack of emphasis on understanding the causes of the individual differences in risk to relapse. Certainly, no studies show 100% persistent remission, and those patients who either fail to respond to the treatment in the first place, or show relapse at follow-up, may be indicative of a fundamental propensity to relapse. Alternatively, they may reflect inter-individual differences in boundary conditions on reconsolidation (see below), thereby suggesting that there is likely to be persistent benefit in those patients who do respond. Moreover, it is not out of the question that the same intervention might induce memory impairment via distinct or a combination of different mechanisms depending on the particular experimental or clinical setting [70].

The reliability of reconsolidation effects

The previous discussion concerns the interpretation of reactivation-dependent amnesia. There is, however, emerging a more fundamental challenge to the reconsolidation literature than alternative theoretical interpretations; namely, whether the fundamental preclinical findings are sufficiently reliable and replicable to warrant translational application. If memory reactivation combined with pharmacological or non-pharmacological treatment does not reliably induce any memory impairment, then the rationale for clinical exploitation may be flawed. As a recent high-profile example, the original demonstration that human motor memory could be disrupted by combining memory reactivation with interference [13] was not replicated in a series of direct and

conceptual replication attempts within a single extensive study [71]. While perhaps it remains unclear whether human motor memories undergo reconsolidation, there are very many studies showing reconsolidation effects in other settings [72], particularly for fear memories. Many of these studies may indeed be sub-optimally designed to allow for the observation of memory recovery [73; see above]. Nevertheless, to suggest that memory reconsolidation, as a wider phenomenon, is invalidated by a single (or even a number) of failed replications suffers from the same risk of over-interpretation as does any assumption that retrieval-dependent memory deficits necessarily reflect reconsolidation impairments [see 74, for example].

Given that retrieval-extinction is the most mature of the reconsolidation-update literature, it is possible to draw some inferences about the replicability of the phenomenon. Some attempts to replicate conceptually the original findings were seemingly unsuccessful [75-78]. The resultant uncertainty in the literature might suggest that attempts to combine memory reactivation with extinction training (and perhaps, by extension, other reconsolidation-update procedures) are not likely to be viable clinically. However, as reviewed earlier, there is a growing literature supporting the likely translational efficacy of reconsolidation-update. Within this framework, the observations of failures to show memory impairments in individual studies should, we argue, not lead to obsessive discussion as to whether reconsolidation-update exists, but rather should be viewed constructively in terms of increasing our understanding of reconsolidation-update and its potential for translational exploitation [79]. The failure of a treatment, pharmacological or behavioral, to impact upon a reactivated memory may result from a lack of efficacy on one of two fronts. Firstly, for reconsolidation impairments to be effective, the memory must be successfully destabilized. Second, the reconsolidation process must be disrupted or hijacked effectively. Therefore, a negative finding may result either from a failure to destabilize the memory or because the treatment does not reliably impair/modify its reconsolidation.

Given the link between reconsolidation and memory updating, only those reactivation sessions that induce memory updating will likely destabilise the existing memory, rendering it vulnerable to pharmacological or behavioural intervention. Many studies have determined parametric conditions under which memories do and do not destabilize [e.g. 25, 45, 48, 80, 81, 82]. While most of these boundary conditions have been identified in rodent studies using a variety of amnestic treatments, there is emerging understanding of the boundary conditions on human fear memory destabilization. First, it has been suggested that memory retrieval in itself is insufficient to trigger fear memory destabilization, as assessed by the impact of propranolol [83]. It appears that there is indeed a requirement for human fear memory updating, conceptualized as an error in prediction about the forthcoming experience during memory reactivation, in order to destabilize the underlying memory [48]. Armed with this understanding, clinical

interventions can be designed such that pharmacological or behavioural updating treatment are only implemented if the memory reactivation procedure has been deemed to have successfully evoked the problematic memory and induced some level of prediction error [84]. Such a prediction error might also be elicited by unexpected presentation of the aversive outcome (as opposed to its unexpected omission following stimulus exposure), as evidenced by the capacity of outcome presentation to destabilize human fear memories within a retrieval-extinction setting [85]. Moreover, personality traits may provide a modulatory impact upon the success of reconsolidation treatments. High trait anxiety attenuated the beneficial reduction in fear following reactivation-related propranolol, which is likely due to the lack of efficacy of the reactivation procedure in destabilizing the fear memory [86]. These insights into modulatory effects on memory destabilization have emerged from studies, in which there has been a successful demonstration of reconsolidation impairment. Replication failures might provide further valuable information concerning the reliability of memory destabilization procedures. The challenge, however, is to disambiguate whether replication failures result from a lack of efficacy in memory destabilization or impairing memory reconsolidation. Advances in our understanding of the neural and cellular mechanisms of memory destabilization may allow some disambiguation, given the nascent ability to enhance destabilization pharmacologically and thereby facilitate reconsolidation impairments [Box 2].

Assuming that a memory is successfully destabilized, a failure to observe a reconsolidation effect may result from a lack of efficacy of the behavioral updating treatment. This may not be a fundamental lack of efficacy, but instead might reflect a "behavioral dosing" effect. In a similar manner to the use of single standard drug doses, regardless of potential individual differences that may impact upon drug response, inter-individual variability is highly likely to impact upon the response to the invariant parameters of extinction (or other updating) training. That is, some individuals (human and non-human) may require greater extinction training post-retrieval, or various forms of it, in order to achieve reliable long-lasting reduction in memory expression. For example, while previous studies failed to demonstrate retrieval-extinction effects on fear-relevant stimuli (such as spider and snake images) using standard extinction [78, 87], a recent study using vicarious extinction (observing another person undergoing extinction) was more efficacious [88]. Moreover, even at the individual level, the degree of behavioural updating required to mitigate the memory will depend upon the strength of the memory in the first place. An appreciation of the potential for such variability, and its consequences for clinical impact, would guide the interrogation of current and future studies in order to identify causes and mitigate/exploit them to improve the efficacy of the treatment. Perhaps indices of original memory strength and the within-session success of update training would be predictive of long-term efficacy.

Concluding remarks

Over half a century ago, the dominant memory paradigm has initially marginalized the reconsolidation phenomenon, positing that consolidation takes place only once in the lifetime of a memory - during its initial formation. This paradigm shifted more than a decade ago, with the discovery of brain circuits mediating memory reconsolidation using well-defined behavioral procedures. Since then, reconsolidation has been described in fine detail spanning all levels of analysis, from molecular, cellular, and physiological, to behavioral and large-scale neural systems, over a spectrum of species, amnesic agents, and behavioural protocols. The fact that reconsolidation interventions may lead to memory weakening, modification or strengthening, is consistent with an adaptive view of reconsolidation: a biological memory mechanism enabling memory updating. Initial support for this idea came from a few key studies showing that new learning during reconsolidation modifies the expression of motor, episodic and emotional memories, and that memory strengthening is mediated by reconsolidation mechanisms. To date, the phenomenon of reconsolidation updating has greatly matured with substantial evidence encompassing various memory systems (motor, episodic, emotion, spatial), valences (negative, positive and neural), species (mice, rats and humans), developmental stages (adolescence and adulthood), and clinical populations (addiction and anxiety).

Reconsolidation remains a topic of intense research, not only for the basic understanding of long-term memory but particularly for the potential application to psychiatric conditions, in which persistent maladaptive memories are a core feature (see Outstanding Questions). The translation of reconsolidation theory to psychiatric practice utilizing pharmacological and behavioral interventions is already underway, yet there remain significant fundamental issues that need to be addressed in order to maximise (or at least fully evaluate) the therapeutic potential – alternative explanations and replication failure. Alternative explanations generally arise from data sets that appear, at first sight, to be inconsistent with the assertion that reconsolidation impairments should be reactivation-dependent and long lasting. Usually, they centre on observations that the memory can be "recovered" via some manner of reminder even after reconsolidation impairment. Our criticism of the alternative explanations is that they tend to over-interpret individual observations, thereby extending an explanation of a single study to the entire literature. We argue that this generalisation of interpretation is both unnecessary and unwarranted. Rather, the central observations that triggered the alternative explanation may be viewed constructively from a clinical perspective. In particular, translational studies will need to test for resilience against recovery more systematically, as it may be difficult to determine *a priori* whether any beneficial effects are truly a result of reconsolidation impairments, and hence are likely to be persistent.

Replication failure encompasses observations that fail to replicate memory impairment as a result of reactivation + treatment. There have been a number of papers purporting to fail to

replicate or extend the reconsolidation-updating phenomenon. These replication failures could be held to provide doubt concerning the phenomenon itself. However, we argue instead, that the conflicting literature provides a rich opportunity to understand more fully the "boundaries" and limitations of reconsolidation updating. The sheer number of positive studies support the existence of the phenomenon, yet the failures to replicate present a valuable insight into how reliably the phenomenon might be exploited for translational benefit by highlighting the critical factors underlying reconsolidation updating. Thus, a deeper analysis of the replication failures, even at a conceptual level, is essential especially since any optimisation of translational application will have to determine the source of failures. In particular, future research should focus on whether the failures represent failure to destabilise the memory or a lack of behavioural updating via the restabilization process. This may be possible by identifying specific markers of memory destabilization and restabilization. Cellular and molecular indications could be utilized to develop pharmacological agents that may aid memory destabilization and restabilization upon need, and system level markers in the human brain may signal effective behavioral manipulations.

All in all, research on behavioral targeting of reconsolidation aligns with the futurist view that non-invasive manipulations may one day make drug therapy obsolete. A second possibility is that there may be a class of psychopathologies that are responsive to non-pharmacological and some to the pharmacological. The third possibility is some individuals may be more responsive to the pharmacological vs non-pharmacological approaches for some psychopathologies than others. Successful translation of the rich reconsolidation literature into clinical applications may critically depend on our ability to describe the processes of memory destabilization and restabilization as separate and complementary targets for pharmacological and behavioral interventions.

Box 1: Alternative interpretations of retrieval-dependent amnesia

Alternative interpretations such as state-dependent learning and unleashed extinction follow a line of challenges to reconsolidation theory (nonspecific drug effects such as lesions [89], state-dependent learning [61], new learning [90], facilitated extinction [91], and retrieval impairment [92]. All of these issues have been explicitly addressed in a previous review and have been refuted on the basis of their inability to account for the richness of data supporting the reconsolidation interpretation [23]. Briefly, the observations of recovery from amnesia do not necessitate a retrieval-impairment view of amnesia as is implicit within the alterative interpretations. Recovery from amnesia is by no means a novel observation and has limited interpretative value [93], as recovery procedures can easily supplement an incompletely disrupted memory [70, 94, 95]. There is also a computational model showing how a partially impaired memory can be strengthened by reminder cues, bringing the amnesic group to parity with the controls [96]. Secondly, many studies have explicitly tested for, and failed to show spontaneous recovery, reinstatement and state-dependent learning [97]. Moreover, non-reconsolidation accounts fail to explain examples where drug treatment can potentiate, rather than impair, the reactivated memory [15, 27, 98]. Such memory enhancements are easily interpreted as potentiation of reconsolidation, but the drug treatment should create a similarly altered internal physiological state to that which is hypothesised to account for memory impairments. While memory enhancement could result from an impairment of extinction, the fact that the same treatment can cause bidirectional effects on memory depending upon the parameters of cue exposure at memory reactivation strongly suggests that competing processes (i.e. reconsolidation vs extinction) must exist [22, 23, 25, 27, 99, 100]. Finally, given that extinction is unique to associative memories, unleashed extinction cannot apply to the wider reconsolidation field.

Box 2: Neural mechanisms of memory destabilization and updating

While reactivation procedures can be designed to maximise the chances of inducing prediction errors, and thereby successful memory destabilization, there remains the challenge of achieving this effectively on an individual basis. This raises the potential utility of pharmacologically enhancing memory destabilization. While there is relatively little understanding of the neurochemical mechanisms of memory destabilization, several processes have been identified [101]. At the intracellular level, there appears to be a requirement for protein degradation at the proteasome [102, 103], protein phosphatase activity [104], CamKII [105] and nitric oxide [106, 107]. At the cell surface, there is a functional involvement of cholinergic [108] and dopaminergic receptors [109], at least for non-fear memory destabilization. Of particular relevance to fear memories are the necessity for cannabinoid CB1 receptor and calcium channel activity in the dorsal hippocampus [110] and NMDA receptor activity (specifically NR2B-containing NMDA

receptors) in the basolateral amygdala [111-114]. We and others have exploited some of these mechanisms to stimulate fear memory destabilization, in order to render effective post-reactivation treatment even under conditions that do not normally trigger reconsolidation [115-117]. Use of pharmacological (partial) agonists to activate CB1 or NMDA receptors during memory retrieval enabled post-retrieval drug treatment to impair the reconsolidation of fear memories. Therefore, even within the realm of behavioral reconsolidation-update there may be cause to incorporate pharmacological treatment in order to maximise the likelihood of successfully destabilizing the maladaptive memory. Our assumption would be that reconsolidation-update should share the same mechanisms of memory destabilization with pharmacological reconsolidation impairments, and this has been shown to be true in the case of the requirement for AMPA receptor trafficking in the amygdala for fear memory destabilization [118, 119]

In the human brain, during post-retrieval extinction, the involvement of the ventromedial prefrontal cortex (vmPFC) and its functional connectivity with the amygdala diminish compared to standard extinction [69]. Following updating, when reconsolidation is complete, subsequent encounters with the conditioned cue elicit lower physiological arousal and reduced amygdala activity and connectivity with vmPFC. Specifically, while amygdala threat memory trace was recovered in a group that underwent standard extinction, the group that underwent extinction during reconsolidation showed no trace recovery in the amygdala even 18 months later [120, 121]. During the phase immediately following the reminder cue and prior to updating, resting-state functional connectivity between amygdala and vmPFC is high, compared to the no-reminder group, and the degree of connectivity predicts the ensuing update-induced reduction in conditioned responses [122]. Together, these findings point to possible markers of reconsolidation updating in the human brain: resting-state functional connectivity as a candidate for memory destabilization, dissociable neural patterns indicating the update process (such as altered amygdala-vmPFC circuitry), and the resulting altered memory representation (such as modified amygdala or hippocampal representation).

TABLE 1 | Some of the paradigms in which behavioral reconsolidation updating has been observed

Experimental paradigm	**Pavlovian threat conditioning** (Monfils et al., 2009 [34]; Schiller et al., 2010, 2013 [35, 69]; Agren et al., 2012a,b [121, 123]; Oyarzun et al., 2012 [124]; Steinfurth et al., 2014 [125]; Johnson & Casey, 2015 [126]; Asthana et al., 2016 [127])
	Pavlovian threat conditioning with fear-relevant stimuli (Golkar et al., 2017 [88]; Thompson & Lipp, 2017 [85])
	Context threat conditioning (Lee, 2010 [36]; Flavell et al. 2011 [38]; Rao-Ruiz et al., 2011 [128]; Pineyro et al., 2013 [64]; Liu et al., 2014 [57])
	Pavlovian reward conditioning (Flavell et al. 2011 [38]; Olshavsky et al., 2013 [42])
	Instrumental reward conditioning (Ma et al., 2012 [129]; Xue, et al., 2012 [39]; Millan et al., 2013 [67]; Sartor & Aston-Jones, 2014 [130])
	Motor sequence learning (Walker et al., 2003 [13])
	Episodic memory (Hupbach et al., 2007 [33]; St Jacques et al., 2015 [131]; Scully et al., 2016 [32])
	Subliminal instrumental conditioning (Pine et al., 2014 [132])
	Spatial memory (Jones et al., 2012 [133])
Updating treatment	**Extinction** (Monfils et al., 2009 [34]; Schiller et al., 2010, 2013 [35, 69]; Flavell et al. 2011 [38]; Agren et al., 2012a,b [121, 123]; Oyarzun et al., 2012 [124]; Steinfurth et al., 2014 [125]; Johnson & Casey, 2015 [126]; Kredlow et al., 2016 [75])
	Vicarious extinction (Golkar et al., 2017 [88])
	Imaginal extinction (Agren et al., 2017 [134])
	Counterconditioning (Olshavsky et al., 2013 [42]; Das et al., 2015 [40]; Goltseker et al., 2017 [41])
	Extinction following unconditioned stimulus reminder (Liu et al., 2014 [57]; Thompson & Lipp, 2017 [85])
	Repeated contextual threat conditioning reactivation concomitant with appetitive stimuli (Haubrich et al., 2015 [135])
	***Tetris* interference** (James et al., 2015 [43])
	Interference with new learning (Walker et al., 2003 [13]; Hupbach et al., 2007 [33]; Jones et al., 2012 [133]; St Jacques et al., 2015 [131]; Scully et al., 2016 [32])
Species	**Mice** (Clem & Huganir, 2010 [118]; Rao-Ruiz et al., 2011 [128]; Graff et al., 2014 [136]; Escosteguy-Neto et al., 2016 [137])
	Rats (Monfils et al., 2009 [34]; Flavell et al. 2011 [38]; Xue et al., 2012 [39]; Olshavsky et al., 2013 [42]; Pineyro et al., 2013 [64]; Liu et al., 2014 [57]; Tedesco et al., 2014 [138])
	Humans (Schiller et al., 2010, 2013 [35, 69]; Agren et al., 2012a,b [121, 123]; Oyarzun et al., 2012 [124]; Liu et al., 2014 [57]; Steinfurth et al., 2014 [125]; Asthana et al., 2016 [127]; Feng et al., 2016 [122]; Scully et al., 2016 [32]; Golkar et al., 2017 [88]; Thompson & Lipp, 2017 [85])
Developmental stages	**Adolescents, humans** (Johnson & Casey, 2015 [126])
	Juvenile/adolescents rats (Jones & Monfils, 2016 [139])
Pharmacological enabling	**Epigenetic priming of memory updating** (Graff et al., 2014)[136]
Clinical populations	**Heroin addicts** (Xue et al., 2012 [39])
	Hazardous Alcoholic drinkers (Das et al., 2015 [40]; Hon et al., 2016 [49])
	Tobacco smokers (Germeroth et al., 2017 [44]
	Spider phobic (Bjorkstrand et al., 2016, 2017 [54, 55]; Telch et al., 2016 [53])

Examples of various experimental paradigms, updating treatments, species, and clinical populations, from studies reporting evidence for reconsolidation updating.

Figure Legend

Fig. 1. The stages of reconsolidation updating. Experiencing a significant event may result in the formation of a long-term memory (in this case, an aversive emotional memory of a threatening dog). Encountering cues associated with the event (such as the red collar), may serve as a reminder that triggers the memory and destabilizes it. Re-stabilization (reconsolidation) of the memory ensues until the memory returns to a stable inactive state. During this time-window, update may occur in several possible ways, for example: extinction, counterconditioning, or interference. These processes may provide new information that is then incorporated into the memory (extinction, counterconditioning), or compete for resources and interfere with the memory's re-storage, thereby hindering subsequent retrievals. The result is an updated memory, in this case devoid of the negative emotional response. In the case of drug-related memories, such updating may result in reduced drug craving. Reconsolidation updating in other memory systems might induce other alterations such as modified memory content. For example, new learning during reconsolidation of episodic memories can result in reduced or enhanced correct retrievals of the episodic items; and new learning during reconsolidation of motor memories can result in altered speed or accuracy of motor performance.

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Glossary

Conditioned stimulus: a previously-neutral stimulus that has been learned to predict an outcome; presentation of the stimulus evokes the memory of the prior learning.

Counterconditioning: the learning of an opposite outcome to that experienced previously (e.g. a stimulus now predicts reward after previously being linked with an aversive outcome).

Destabilization: the active transfer of a retrieved memory into an unstable state upon the presentation of a reminder, such that the memory will decay if it is not actively restabilized.

Extinction: the presentation of a conditioned/learned stimulus now in the absence of the previously-associated outcome; results in the temporary decline of subsequent memory expression.

Reactivation: re-exposure to memory reminders, which may result in destabilization of the previously-learned neural representation of memory.

Reactivation-extinction (retrieval-extinction): the combination of memory reactivation (usually via a reminder that results in memory retrieval) and, after a brief interval, subsequent extinction.

Reconsolidation: the active process that is required to restabilize a reactivated/destabilized memory; disruption of reconsolidation results in memory impairment, while new information is incorporated during reconsolidation into an updated memory.

Retrieval: a reminder results in retrieval of the previously-learned memory; the term encompasses the multiple processes from reactivation of the neural memory representation through to behavioural expression of the memory.

Unconditioned stimulus: a motivating outcome (aversive or rewarding), which promotes learning about a conditioned stimulus that predicts the outcome.

State-dependent learning: the embedding of a learned memory within the physiological state present at the time, such that retrieval of the memory is most successful if the physiological state is reinstated.