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THEORETICAL/REVIEW

Appraising reconsolidation theory and its empirical validation

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Abstract
Re-exposure to elements of prior experiences can create opportunities for inducing amnesia for those events. The dominant theoretical framework posits that such re-exposure can result in memory destabilization, making the memory representation temporarily sensitive to disruption while it awaits reconsolidation. If true, such a mechanism that allows for memories to be permanently changed could have important implications for the treatment of several forms of psychopathology. However, there have been contradictory findings and elusive occurrences of replication failures within the "reconsolidation" field. Considering its potential relevance for clinical applications, the fact that this "hot" research area is being dominated by a single mechanistic theory, and the presence of unexplainable contradictory findings, we believe that it is both useful and timely to critically evaluate the reconsolidation framework. We discuss potential issues that may arise from how reconsolidation interference has typically been deducted from behavioral observations, and provide a principled assessment of reconsolidation theory that illustrates that the theory and its proposed boundary conditions are vaguely defined, which has made it close to impossible to refute reconsolidation theory. We advocate for caution, encouraging researchers not to blindly assume that a reconsolidation process must underlie their findings, and pointing out the risks of doing so. Finally, we suggest concrete theoretical and methodological advances that can promote a fruitful translation of reminder-dependent amnesia into clinical treatment.

Keywords Memory reconsolidation · Theory specificity · Reverse inference · Open science · Clinical translation

Introduction

Emotional memories play an important role in several forms of psychopathology, including anxiety disorders, post-traumatic stress disorder (PTSD), and addiction. Targeting such unwanted memories is thus highly interesting from a clinical perspective (Beckers & Kindt, 2017). It has repeatedly been demonstrated in the lab that forgetting can be induced by combining a reminder to a previously acquired memory with any of a number of electrophysiological, pharmacological, genetic, or behavioral manipulations (Misanin et al., 1968; Nader et al., 2000; Przybyslawski & Sara, 1997). We refer to this type of forgetting as "reminder-dependent amnesia" henceforth. We choose this terminology because it does not commit to a given underlying process. It merely refers to a lack of memory expression (i.e., amnesia) that results from the combined application of a procedure aimed to probe a previously established memory (i.e., the reminder) and some sort of amnestic intervention. By now, there have been countless demonstrations of such effects in the lab, both in humans and in non-human animals (for reviews and a meta-analysis, see, e.g., de Oliveira Alvares & Do-Monte, 2021; Elsey & Kindt, 2017; Monfils & Holmes, 2018; Nader, 2015; Paulus et al., 2019; Pigeon et al., 2022). However, translational studies in patient populations have yielded mixed results, suggesting that it is challenging to effectively apply reminder-dependent amnesia in clinical practice, and highlighting the need to advance our understanding of when, how, and why such amnesia may occur (Beckers & Kindt, 2017).

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Here, we explain why it is conceivable that such theoretical progress has been impeded by the way reconsolidation theory is currently being formulated and empirically tested. We maintain that researchers should be careful in assuming that their findings must rely on a theoretical "reconsolidation" process, and labelling their results accordingly. After introducing reconsolidation theory, which is the dominant theoretical framework for reminder-dependent amnestic effects, we elaborate on two main issues that need to be resolved before heavily investing in further clinical translation of reminder-dependent amnesia. Although we mainly focus on theoretically oriented barriers and possible solutions, we also describe how methodological approaches can play an important role in moving the field forward. As an aside, note that many of the issues described below are by no means unique to this particular field. As such, many of our points are of relevance for other (behavioral neuro)sciences as well.

The currently dominant theoretical framework posits that reminder-dependent amnestic effects rely on the occurrence of memory destabilization and reconsolidation. More specifically, reconsolidation theory assumes that a destabilized or active memory trace is temporarily sensitive to modification until the memory is presumably reconsolidated (Nader et al., 2000; Przybyslawski & Sara, 1997) (Fig. 1). Several manipulations are thought to interfere with memory reconsolidation if administered while the memory is in an active state, resulting in a disrupted (or enhanced) memory. Functionally, it is assumed that reconsolidation serves to allow for the updating of memories by providing the opportunity for incorporating novel information into an existing memory trace (Exton-McGuinness et al., 2015).

The introduction of reconsolidation as a theoretical framework has greatly promoted and inspired new research, and there is an abundance of empirical evidence that seems to be in accordance with the existence of a reconsolidation-like mechanism. Beyond initial findings with fear memories, the field has expanded enormously, including applications to different types of memory and using an extensive variation of manipulations in a wide range of species (Nader, 2015). As a result, the adoption of reconsolidation-based procedures has been touted as a highly promising approach for the clinical treatment of several forms of psychopathology. For instance, a number of clinical trials have claimed to test reconsolidation blockade in people with (sub)clinical anxiety, mainly phobias and post-traumatic stress disorder (PTSD). Some of these studies have found clinically significant beneficial effects of a reminder combined with an amnestic intervention like, for example, propranolol (e.g., Brunet et al., 2018; Soeter & Kindt, 2015), while other studies showed mixed findings (e.g., Bolsoni et al., 2022; Brunet et al., 2008; Roullet et al., 2021; Surís et al., 2010), and yet others found no effects (e.g., Elsey et al., 2020; Elsey & Kindt, 2021; Raut et al., 2022; Surís et al., 2013; Tang et al., 2021; Wood et al., 2015). Of note, Brunet et al. (2008) found statistically significant effects for physiological measures (skin conductance and heart rate) during traumatic imagery, but not for actual PTSD symptoms (Brunet et al., 2011). For several other studies that claimed to test reconsolidation-based therapy, it is difficult to assess their outcome, for example because they lacked a placebo control (Brunet et al., 2011; Brunet et al., 2021; Gahr et al., 2014; Kindt & van Emmerik, 2016; Thierrée et al., 2020) or only included control subjects who had explicitly refused the treatment (Brunet et al., 2011). Of note, the overview above includes clinical trials that aimed to disrupt reconsolidation using either pharmacological or electroconvulsive interventions, and does not consider post-reminder extinction studies, given that these have a slightly different purpose that centers on integrating an extinction memory into the initial fear memory, rather than disrupting this initial fear memory (Monfils et al., 2009).

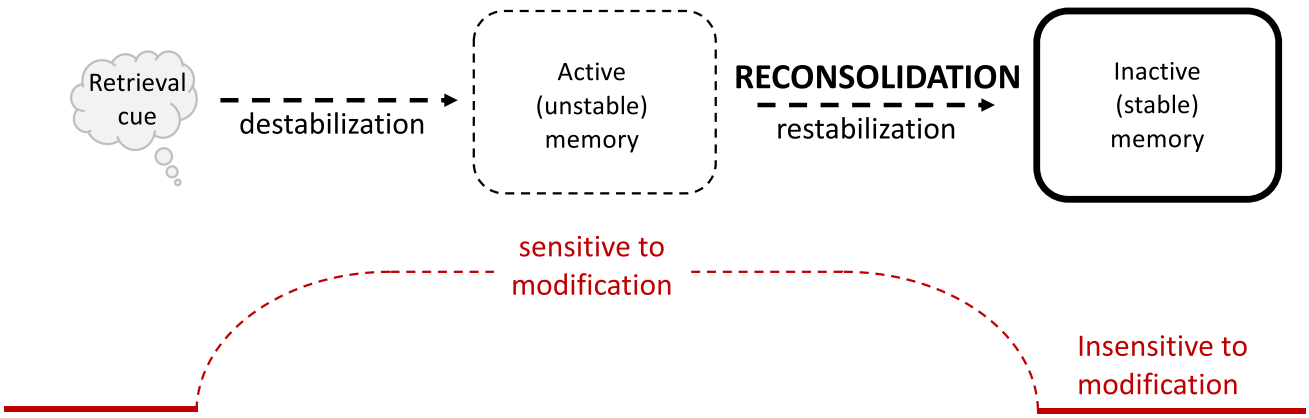

Fig. 1 Schematic representation of reconsolidation theory

Although reconsolidation theory has dominated the field, it has not been free from debate. It has been suggested that not all behavioral effects observed after combining a reminder with an amnestic manipulation can be attributed to reconsolidation interference (Alfei et al., 2020; Alfei et al., 2021; Boddez et al., 2020; Cahill et al., 2019; Gisquet-Verrier et al., 2015; Lattal & Abel, 2004; Riccio et al., 2006; Rudy, 2006). In addition, there have been a considerable amount of failures to conceptually or exactly replicate previously published studies that appeared to demonstrate memory reconsolidation interference (Biedenkapp & Rudy, 2004; Bos et al., 2014; Careaga et al., 2015; Chalkia, Schroyens, et al., 2020a; Dawson & McGaugh, 1969; Elahi et al., 2020; Hardwicke et al., 2016; Luyten et al., 2021; Luyten & Beckers, 2017; Schroyens, Alfei, et al., 2019a; Thome et al., 2016). This limited list of replication failures may be thought to be overshadowed by the abundance of publications that do report amnestic effects, but it should be noted that the literature may offer a distorted picture regarding the frequency of null findings (Schroyens et al., 2021). Importantly, reconsolidation theory presently cannot illuminate which factors explain the negative results.

Given the above-mentioned characteristics of the field (i.e., a popular research area dominated by a single mechanistic theory, contradictory findings, several elusive occurrences of replication failures, and potential relevance for clinical applications), we believe that it is useful to critically evaluate the reconsolidation framework.

The current review discusses how empirical behavioral studies relate to the process and theory of reconsolidation, and describes how reconsolidation theory and its empirical validation could be improved (see Fig. 2 for an overview of the three main topics that we address). In brief, the core assumptions of reconsolidation theory entail that combining a reminder session with a manipulation can induce behavioral changes that rely on the occurrence of memory destabilization and reconsolidation (Fig. 2, colored boxes). The first issue that we address is reverse inference, i.e., attributing observed effects to the occurrence of unobservable processes such as destabilization or reconsolidation (Fig. 2, ①), and why such reverse inference may hinder effective application and development of reconsolidation theory (Fig. 2, ②). We then elaborate on how the use of auxiliary assumptions, consisting of a range of vaguely defined boundary conditions, has allowed researchers to explain most possible outcomes

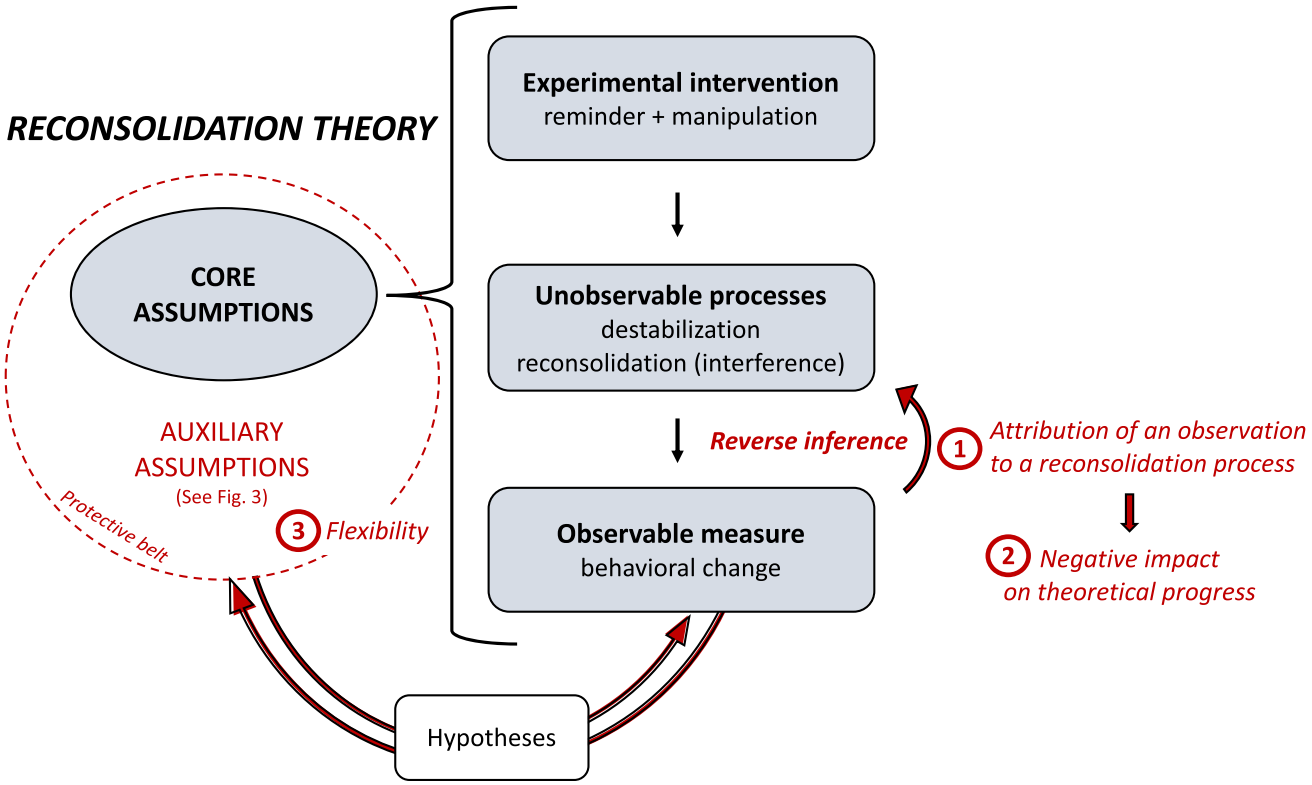

Fig. 2 The current review evaluates how empirical observations have been related to the unobservable processes of memory destabilization and reconsolidation ① and the impact that such practices may have had on the application and development of the theory of reconsolidation ②. A principled evaluation of reconsolidation theory examines to which extent its core and auxiliary assumptions allow for precise and testable predictions ③. Parts of the figure were inspired by Poldrack (2006) and by Oberauer and Lewandowsky (2019)

with recourse to reconsolidation theory and protect the theory from refutation (i.e., auxiliary assumptions form a "protective belt" around the theory's core assumptions; Fig. 2, ③) (Lakatos, 1976).

Reconsolidation from an empirical perspective

Can we infer reconsolidation interference from observed behavior?

Reconsolidation is most often inferred from behavioral results that illustrate susceptibility to an amnestic manipulation after a reminder (Fig. 2, ①). In other words, it is concluded that the *unobservable* process of reconsolidation has occurred on the basis of an *observed, behavioral* outcome. Below, we elaborate on two issues that should be considered when making inferences about an unobservable process based on observed behavior, and assess the state of affairs in the reconsolidation field. The first issue, which is specifically related to reconsolidation theory, deals with the criteria that have been proposed to establish whether an observed effect may represent reconsolidation interference. The second issue, which is applicable to behavioral sciences in general, relates to the caution that is required when inferring hypothetical processes based on observation.

Table 1 provides an overview of several criteria that have been proposed to evaluate whether an observed behavioral effect may effectively represent reconsolidation interference (Elsey et al., 2018; Hardwicke, 2016; Kroes et al., 2016; Tronson & Taylor, 2007).

The question at hand is to which extent those criteria are met in studies that claim to demonstrate memory reconsolidation. Hardwicke (2016) and Elsey et al. (2018) have provided valuable insights into this issue by evaluating published studies on reminder-dependent amnesia in human subjects across different types of memories and interventions (Table 1). To our knowledge, such an investigation has not yet been performed systematically for studies with non-human animals. Both reviews revealed that only a minority of reconsolidation studies had assessed the proposed

Table 1 Fulfillment of various criteria has been suggested to be necessary for inferring reconsolidation interference from observed behavior

	Criterion		Hardwicke (2016)	Elsey et al. (2018)
	Required at procedural level	Predicted observation		
A	Do intervention at least 1 day after initial encoding	NA	yes	yes
B	Test Reminder x Manipulation interaction	Combination of reminder and manipulation is crucial to observe the effect	yes	yes
C	Do manipulation after reminder	NA	yes	no
D	Vary reminder-manipulation interval	No effect when manipulation takes place after termination of putative reconsolidation period	yes	yes
E	Perform STM and LTM test	Effect of interest is observed at LTM test, but not at STM test*	yes	yes
F	Assess specificity of the effect	Manipulation only affects the allegedly reactivated memory	no	yes
G	Assess longevity of the effect (e.g., recovery after time, reinstatement, renewal, …)	No recovery observed	yes	no**

The last two columns indicate for each criterion whether it was included in the assessments by Hardwicke (2016) and Elsey et al. (2018)

(A) initial memory trace should have been consolidated (Nader et al., 2000), but see Dudai and Eisenberg (2004);

(B) provided by the same or a closely related study;

(C) pre-reactivation interventions leave more room for alternative explanations and are to be avoided if a study aims to demonstrate reconsolidation interference;

(D) the putative duration of this sensitivity time window varies between studies, ranging from 1 to 6 h (Bustos et al., 2006; Nader et al., 2000);

(E) testing for behavioral effects should occur after the assumed reconsolidation process is completed and rule out the presence of any acute (e.g., drug) effect on behavior (long-term memory (LTM) test); additional testing shortly after the manipulation can serve as a negative control, given that interference should only become apparent after termination of the alleged reconsolidation period (short-term memory (STM) test; *except for post-reminder extinction learning, when similar STM and LTM performance is expected);

(F) the obtained effect should be specific to the reactivated memory

(G) behavioral effects should be permanent for a reconsolidation account to be valid (Hardwicke, 2016; Lattal & Abel, 2004; Miller, 2021; Monfils et al., 2009; Tronson & Taylor, 2007), although some claim that it is possible for reconsolidation interference to alter only a portion of the destabilized memory trace, allowing for at least partial recovery of memory performance (Amaral et al., 2008; Elsey et al., 2018; Gold & King, 1974; Nader & Wang, 2006)

**Elsey et al. (2018) mention that testing for the longevity of the effect may provide insights, but highlight that such insights cannot count as refutation or proof of memory reconsolidation interference per se (see section *Long-Term Effects of Reconsolidation-Based Interventions and the Storage Versus Retrieval Debate* of Elsey et al., 2018).

criteria to infer reconsolidation interference from behavioral findings (see Elsey et al. (2018), Fig. 1; and Hardwicke (2016), Fig. 2.2). More specifically, none of the 168 studies reviewed by Hardwicke (2016) met all proposed criteria, and most key criteria (i.e., B, D, E, F, and G from Table 1) were assessed in less than half of the studies. Elsey et al. (2018) reached a similar conclusion, with only two out of 91 studies assessing all the proposed criteria. Furthermore, Hardwicke (2016) and Elsey et al. (2018) identified several cases where some of the relevant criteria were explored, but not fulfilled (i.e., the observed results were not in line with what would be assumed on the basis of reconsolidation theory). Both reviews thus suggest that many of the published human studies' positioning within a reconsolidation framework cannot be justified based on the adopted experimental designs.

In general – and this is by no means unique to the reconsolidation field, but is basically true for any science built on observation – we should be cautious when inferring the involvement of an unobservable process from an observed effect (e.g., a change in conditioned responding, task performance, or brain activity). A hypothetical example of such reverse inference (i.e., from observed effect to unobservable process) in the reconsolidation field can be as follows (adapted from Poldrack (2006)):

(1) In study A, the presentation of a retrieval cue followed by drug X administration resulted in a decrease in fear responding compared to vehicle controls.
(2) In previous studies, an observed decrease in fear responding observed after reminder + drug Y administration could be reasonably attributed to reconsolidation disruption.
(3) Therefore, the decrease in fear observed in study A also demonstrates reconsolidation disruption by drug X.

Although it has been acknowledged that reverse inference can be useful for scientific progress by suggesting novel hypotheses that can then be tested empirically, such inferences are only acceptable if the observation can occur if and only if the process of interest is engaged (De Houwer, 2011; Poldrack, 2006). This implies that reminder-dependent behavioral effects cannot be equated to the presence of reconsolidation interference per se (Alfei et al., 2020; Alfei et al., 2021; Gisquet-Verrier et al., 2015). In addition, it should be acknowledged that behavioral studies can never prove the occurrence of a reconsolidation process, so caution is always required when making statements related to reconsolidation.

In sum, inferring reconsolidation interference based on observed behavioral results requires caution because such reverse inference is often unwarranted (De Houwer, 2011; Poldrack, 2006). However, such caution seems to be lacking in much of the reconsolidation literature; two comprehensive reviews illustrate that reconsolidation has often been concluded based on behavioral data without actually testing it as a potential mechanism (i.e., essential criteria to make the bridge between behavior and reconsolidation as an underlying mechanism have not been assessed) (Elsey et al., 2018; Hardwicke, 2016). The following section clarifies why such practices may pose problems for theoretical progress.

Equating reconsolidation interference to observed behavior may impede theoretical progress

Theoretical progress is crucial to obtain a better understanding of when and how amnestic effects occur, which can greatly advance its proposed application in clinical settings. Below we explain why it is conceivable that the unconditional and often unjustified adherence to reconsolidation as the mechanism at play in observations of reminder-dependent amnesia (as discussed in the previous section) has likely impeded such progress.

First, given the complex nature of reminder-dependent amnesia, "reconsolidation" may well have been used to describe observations that in reality relied on a variety of processes (De Houwer, 2011). This implies that some of the assumptions embedded in reconsolidation theory may have been inferred from observations that were in fact the result of a process different from reconsolidation (Fig. 2, ②). This is also problematic for the emerging clinical trials that aim to exploit the notion of reconsolidation interference but often lack the control conditions mentioned in Table 1, and which may then in turn give rise to unjustified subsequent trials. In addition, studies that were designed based on reconsolidation theory (e.g., by using certain reminder conditions that are assumed to induce memory destabilization and sensitivity to manipulation) may have failed to obtain an anticipated effect because the adopted procedure actually induced a process other than reconsolidation, to which different boundary conditions apply (Fig. 2, ②).

A second way in which adherence to the notion of reconsolidation may be detrimental for theoretical progress is by slowing down the exploration of other viable explanations (De Houwer, 2011). For example, researchers may have been discouraged to investigate alternative explanations, such as state-dependent learning, counterconditioning, or enhanced extinction, in the context of reminder-dependent amnesia because this notion did not fit within the dominant reconsolidation framework. A comprehensive overview of these alternative explanations falls outside of the scope of this review, but much of the debate can be brought back to a storage versus retrieval failure view of amnesia. Indeed, it is typically impossible to discern whether observed reminder-dependent amnesia results from modification or erasure of the original memory trace (as posited by reconsolidation theory) or from the mere failure to retrieve an otherwise

intact memory (i.e., the originally acquired information is still stored in the brain but is not presently accessible). The state-dependency account suggests that amnesia may result from a retrieval failure due to incongruency between a subject's internal state at the time of the reminder versus at the time when the memory is tested (Gisquet-Verrier et al., 2015). The counterconditioning explanation assumes that the reminder session (which, e.g., in fear conditioning research, typically consists of presenting a conditioned cue without its former outcome) installs a competing association alongside the original memory trace (Haubrich et al., 2015). Given that many reminder sessions are operationally equivalent to an extinction trial, it has been suggested that they may entail extinction learning, again assuming that the original memory remains intact, but that a competing, inhibitory memory trace is formed, which may then lead to reminder-dependent amnesia at test (Lattal & Abel, 2004). To be clear, the abovementioned alternative hypotheses can currently explain a subset of the observed effects at most, and should undergo the same scrutiny as proposed for reconsolidation theory. That said, in many instances researchers fail to even consider these alternative explanations for their observations of reminder-dependent amnesia.

Finally, assuming reconsolidation as the underlying mechanism encourages researchers to neglect or explain away evidence against the occurrence of reconsolidation-based mechanisms (De Houwer, 2011). Indeed, as is discussed in the next section, the flexible nature of proposed boundary conditions of the theory has enticed researchers to put forward such conditions to explain contradictory outcomes with recourse to reconsolidation theory.

Reconsolidation from a theoretical perspective

Whereas the previous section dealt with the inference of a reconsolidation process from empirical results and the potential pitfalls in linking behavioral observations to a neurobiological construct, the current section focuses on reconsolidation theory itself and how it can and has been used to accommodate a wide range of empirical results. In what follows, we will first elaborate on why theories should be specific and next illustrate that reconsolidation theory lacks such specificity.

Specificity as a key criterion of good theory

A scientific theory is composed of ideas that aim to predict and explain observed phenomena, and empirical research is required to test whether a theory actually fulfills this aim. During the iterative process of theory testing and refinement, a range of background or auxiliary assumptions are typically proposed to form the bridge between empirical observation and theory (Lakatos, 1976; Popper, 1959). Those auxiliary assumptions are not part of a theory's core assumptions, but rather allow researchers to interpret experimental data in light of the theory; such as, for example, assumptions on how to interpret freezing responses in rodents or considerations about the characteristics of a memory when assessing its malleability. Auxiliary assumptions may vary between experiments without jeopardizing the theory's core assumptions, and can therefore be used to protect the theory's "hard core" from refutation. However, it has been proposed that changes to those auxiliary assumptions are only adaptive if they can be confirmed empirically and if they allow us to better explain or predict the phenomenon at hand (Lakatos, 1976).

An important aspect of a good theory is its specificity, allowing for the derivation of precise predictions that can be tested experimentally. However, it has been argued that most theories in the behavioral sciences are weak, given that they are too vague to allow for clear predictions (e.g., concerning the conditions under which the effect occurs or the magnitude of the effect) (Fried, 2021; Gieseler et al., 2019; Grahek et al., 2021; Meehl, 1990; Oberauer & Lewandowsky, 2019; Szollosi & Donkin, 2021). If a theory is poorly specified, it leaves room for researcher degrees of freedom and subjective interpretation of obtained results (i.e., flexibility), which may eventually result in the problem that basically any observation can be explained by the theory. The less specified the theory is, the more researchers can rely on the use of (new) auxiliary assumptions. A failure to observe an effect can then be attributed to auxiliary assumptions, such as the proposal of a novel moderator, without questioning the theory's core assumptions (Gershman, 2019). As a result, any empirical test addressing the theory has limited diagnostic value because it becomes unclear when (if ever) a statistically significant effect falsifies or corroborates the theory.

The use of poorly specified theories further implies that the prior probability of any derived hypothesis being true is low (in other words, the predicted effect has a low base rate of occurrence), which has been shown to increase the chance of obtaining false-positive results when using conventional criteria for null hypothesis testing (Oberauer & Lewandowsky, 2019). In addition, without the presence of a well-specified theoretical framework, one cannot predict under which exact conditions an effect will (not) replicate, and any replication failure does not allow us to draw conclusions about the theory. As such, it has been argued that the use of unspecific and flexible theories and/or auxiliary assumptions plays a major role in replicability issues in general (Klein, 2014; Oberauer & Lewandowsky, 2019; Szollosi & Donkin, 2021; Trafimow & Earp, 2016).

A principled evaluation of reconsolidation theory

In the current section, we evaluate the *specificity* of reconsolidation theory (Fig. 2, ③), seeing that this is a key aspect of good theory, as explained above.

Reconsolidation theory posits that combining a reminder session with a manipulation can induce a change in mnemonic performance. The theory's core assumptions entail that (1) the reminder session can result in memory destabilization (making the memory temporally sensitive to modification) and the requirement of reconsolidation, and (2) the manipulation interferes with the reconsolidation process to induce the observable behavioral effect; or in some cases, it is assumed that the presented information becomes incorporated in the destabilized memory trace, resulting in an updated memory (Haubrich et al., 2015; Monfils et al., 2009). In the current literature, empirical testing of the predictions derived from reconsolidation theory employs a wide range of procedures with different reminder sessions and manipulations, and the theory predicts that an effect can be observed in some cases, without clearly specifying the conditions under which the effect should occur (Oberauer & Lewandowsky, 2019). For instance, it appears that there is considerable flexibility in the type of manipulations that are deemed effective. Reconsolidation, like consolidation, is assumed to entail protein synthesis-dependent memory storage. In line with the involvement of signalling pathways that are thought to coordinate protein synthesis, several pharmacological and genetic manipulations related to such pathways have been used to interfere with alleged memory reconsolidation (e.g., targeting noradrenergic or glutamatergic receptors, kinases, transcription factors, or immediate-early gene expression). However, a wide range of manipulations that have *not* been linked to those signalling pathways have nevertheless been claimed to also interfere with reconsolidation (e.g., targeting serotonergic, cannabinoid, histamine, oxytocin, adenosine, GABA and opioid receptors, or various types of hormones, peptides, cytokines, and toxins) (Schroyens et al., 2021) without specification of how the drugs' mechanism of action is (indirectly) linked to the putative process of reconsolidation. As discussed in the next paragraphs, such flexibility also applies to the behavioral parameters that are being used to induce alleged memory destabilization. This illustrates that the core assumptions of reconsolidation theory leave quite some room for labeling diverse reminder-dependent behavioral effects as being instances of reconsolidation interference, rather than providing a clearly demarcated scope. In other words, any study combining a reminder and a manipulation and showing a change in behavior is typically seen as being in line with reconsolidation theory, whereas a study that fails to observe such an effect does not necessarily question the theory's core assumptions; it merely reflects that the adopted procedure (or procedural details) cannot be used to obtain the effect (Oberauer & Lewandowsky, 2019). Hence, auxiliary assumptions, mostly consisting of proposed moderators or boundary conditions on memory destabilization, can be used to provide a seemingly acceptable explanation for many results. As illustrated below, this state of affairs is problematic due to the flexible properties of the proposed boundary conditions themselves.

Studies that parametrically manipulated proposed boundary conditions on reconsolidation have provided important insights into the conditions required for obtaining reminder-dependent behavioral effects. In particular, the intensity and type of training, the duration of the training-manipulation interval, the amount of novel information during the reminder session, and the occurrence of extinction learning have received empirical support (see Fig. 3) (Eisenberg, 2003; Hupbach et al., 2011; Kwak et al., 2012; Merlo et al., 2014; Milekic & Alberini, 2002; Pedreira et al., 2004; Sevenster et al., 2014;Suzuki, 2004 ; Wang et al., 2009 ; Winters et al., 2009). This richness in data and experimental methods can be seen as a strength, especially when they fit in a systematic and appropriately controlled approach.

However, it should be acknowledged that most of those moderators rest on *mixed empirical evidence*, because not all studies have found support for their existence, and the exact characteristics of the boundary conditions seem to differ between studies. For example, the time interval between training and reminder session (i.e., memory age) over which memories remain sensitive to a post-reminder manipulation varies substantially between studies (e.g., sensitivity up to 2 days after training (Litvin & Anokhin, 2000); up to 3 but

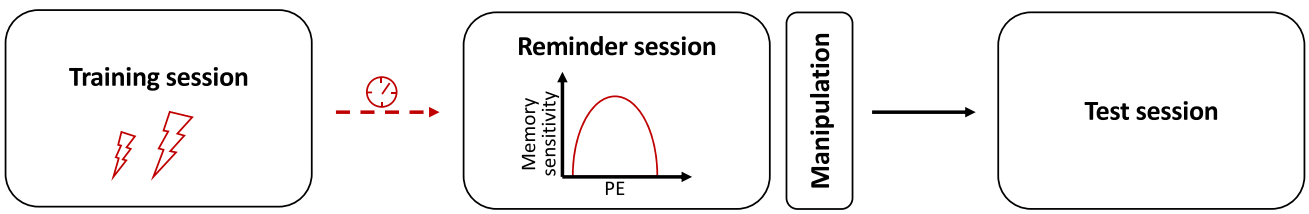

Fig. 3 Commonly-proposed boundary conditions on memory destabilization and subsequent reconsolidation include the strength of training, the time interval between training and the reminder session, and the amount of prediction error (PE) induced during the reminder session

not 7 days (Eisenberg & Dudai, 2004); up to 7 but not 14 days (Milekic & Alberini, 2002); up to 21 but not 56 days (Suzuki, 2004), and no evidence for such temporal gradient was found in other studies when the reminder took place 1 or 14 days after training (Nader et al., 2000) or 3, 15, or 45 days after training (Debiec et al., 2002) (i.e., memory sensitivity did not change over time). Another widely accepted boundary condition is the strength of training, which is typically manipulated by varying the intensity, duration, or number of presentations of the unconditioned stimulus (in case of classical conditioning) or the length of the training session (Winters et al., 2009), through pre-learning stress induction (Espejo et al., 2016), or by pharmacologically enhancing noradrenergic activity around the time of learning (Gazarini et al., 2015). Yet, the classification of a training session as "weak" or "strong" varies considerably between studies. For example, a foot shock of .8 mA has been used in mice to induce strong – difficult to destabilize – contextual fear memory (Kwak et al., 2012), whereas roughly the same intensity (two shocks of .75 mA) has been used as the "weak training' – easy to destabilize – condition in another study (Suzuki, 2004). Individual differences may partially account for variations in the effects of shock intensity (what is "weak" for one animal may be "strong" for another), but this does not detract from the fact that such parametric factors are highly flexible, and thus cannot easily define specific boundary conditions. The mixed observed results regarding the role of boundary conditions have led to the notion that memory-related factors (such as age and strength) may operate as boundary conditions *only under certain circumstances* (e.g., depending on several other factors of the adopted experimental procedure). In addition, it has been illustrated that boundary conditions interact with each other and that they can be overcome, for example, by modifying the duration of the reminder session, prolonging the learning-reminder interval, or adding novel information to the reminder session (Suzuki, 2004; Wang et al., 2009; Winters et al., 2009). Thus, although the role of memory age and strength in memory sensitivity has been illustrated experimentally, it is unclear when exactly those factors will or will not prevent alleged memory destabilization.

Apart from memory age and strength, behavioral studies have suggested that the occurrence of memory malleability relies on the presence of novel information or surprise during the reminder session and depends on the degree of mismatch between predicted and observed events (i.e., *prediction error* (e.g., Fernandez et al., 2016; Gershman et al., 2013; Sevenster et al., 2013; Sevenster et al., 2014; Vaverková et al., 2020). It has been put forward that there is only a small window during which a memory is assumed to destabilize, that is, under conditions that evoke an optimal degree of prediction error (Cassini et al., 2017) (Fig. 3). Nevertheless, there is no specification of what constitutes an optimal degree of mismatch for achieving the assumed destabilization, partly because this is presumed to be highly dependent on a range of other factors such as the preceding training conditions. In fact, finding the appropriate reminder conditions to achieve memory sensitivity seems to be a matter of trial and error. For example, when considering published rodent studies using comparable contextual fear conditioning procedures, a wide variety of different durations of unreinforced context re-exposure has been found to allow for a behavioral change by post-reminder treatment (Schroyens et al., 2021), illustrating that optimal conditions can vary considerably between studies.

An additional difficulty is that prediction error cannot be measured directly, nor is it clear how it should be implemented during the reminder session. This uncertainty has contributed to the flexibility in the adopted experimental designs that have been claimed to induce prediction error. In case of classical conditioning, a mismatch between initial learning and reminder conditions is typically effectuated by omitting the predicted outcome during presentation of the conditioned stimulus (e.g., presenting the conditioned cue without the shock with which it was paired during training). The degree of prediction error has been manipulated by varying the amount of unreinforced trials or the duration of the unreinforced reminder session (for more examples of prediction error induction see Alfei et al. (2015) and Díaz-Mataix et al. (2013)). For other types of memories, such as episodic memory, it is less straightforward how to implement prediction error in the reminder session. Terminating a previously watched video fragment before it has finished, ending a test trial before the participant has had the chance to perform the response, recalling objects that were stored in a basket by re-exposure to the same basket have all been assumed to induce prediction error because the reminder session is a partial, but not full, recap of the training session (Sinclair & Barense, 2019). On the other hand, there are several published studies that were not actually designed to induce prediction error given that training and reminder conditions were very similar, such as a reinforced retrieval trial identical to the training session (Duvarci & Nader, 2004), presentation of images from a previously watched trauma film (James et al., 2015), or a simple recall task (Chan & LaPaglia, 2013), and yet, a reconsolidation-dependent effect was reported.

Overall, the commonly proposed boundary conditions on memory destabilization cannot be clearly operationalized (i.e., they are abstract concepts that do not lend themselves to being quantified by empirical observation) or implemented (i.e., the application of each boundary condition varies considerably between studies). Due to those characteristics, boundary conditions *cannot be translated into specific criteria that can be used to make precise predictions* about when memories will become susceptible to change. Rather,

they contribute to the flexibility that allows the linking of many behavioral observations to reconsolidation theory. Indeed, in practice, failures to observe an anticipated reconsolidation-dependent effect have typically been attributed to the unintended presence of (unknown) boundary conditions on memory destabilization (e.g., the memory might have been too strong or the amount of prediction error might have been inappropriate, also in our own work (Schroyens et al., 2017; Schroyens, Alfei, et al., 2019a)). The proposed moderators of the effect are thus used to protect reconsolidation theory from being contradicted and can allow researchers to explain away inherently conflicting findings with recourse to reconsolidation theory. This, in turn, has made it difficult to conclude whether an empirical observation is consistent or inconsistent with the theory.

Future directions

Distinguishing observed behavior from unobservable underlying processes

As previously suggested for this domain (Miller, 2021; Rudy, 2006) and for empirical behavioral research in general (De Houwer, 2011; Vahey & Whelan, 2016), we maintain that unobservable mechanisms, such as reconsolidation interference, should be clearly distinguished from observed behavioral effects. As such, the term reconsolidation should exclusively be used to refer to a theoretical concept, whereas behavioral effects should be expressed purely in terms of preceding environmental changes and the accompanying observations (De Houwer, 2011; Miller, 2021); for example, "a decrease in fear responding resulting from unreinforced presentation of a conditioned cue followed by anisomycin injection." In this regard, the term "reminder-dependent amnesia" may be a more appropriate label to refer to these behavioral effects given that it remains uncommitted to any underlying process. If reconsolidation interference is raised as a possible neurobiological process underlying an observed behavior, the suggested criteria outlined above (see Table 1) need to be considered and alternative explanations ought to be ruled out or acknowledged. We do not intend to argue that all research on reminder-dependent manipulations should necessarily aim to test whether or not reconsolidation can account for the results. We do claim that if a study is presented within a reconsolidation framework, it should be appropriately designed (in accordance with the proposed list of criteria) to investigate reconsolidation interference as a possible mechanism, and, in any case, behavioral effects should never be equated with the occurrence of a reconsolidation process.

Increasing the precision (and falsifiability) of theory and hypotheses

Enhancing awareness and *acknowledging the flexibility* inherent to reconsolidation theory can be helpful and discourage researchers from (mis)using boundary conditions to explain most results with recourse to reconsolidation theory. Furthermore, it can promote the adoption of a more critical perspective on reconsolidation theory, and enhance openness to alternative explanations. However, merely acknowledging the limitations of reconsolidation theory will not in itself lead to greater progress. Rather, the ultimate aim should be to *formulate theories in a more specific way.* This in turn allows for the derivation of specific hypotheses that are able to challenge and improve the theory in case of disconfirmation by empirical data. An emerging approach to make more precise predictions is the use of computational models (Grahek et al., 2021; Oberauer & Lewandowsky, 2019; but see Fiedler, 2017). Rare examples of such approaches exist in the reconsolidation literature (Gershman et al., 2017; Osan et al., 2011; Sederberg et al., 2011), with each of the proposed computational models focusing on a specific subset of data within the reconsolidation field. However, as illustrated in the next paragraph, building such a concrete theoretical framework for reminder-dependent effects may be challenging at present, given that some of the basic findings (e.g., those that have inspired reconsolidation theory) have proven difficult to replicate.

Establishing a reliable empirical base to inform theory development

Some researchers found amnesia when electroconvulsive shock was given after re-exposure to a previously conditioned tone (e.g., Misanin et al., 1968; Schneider & Sherman, 1968), whereas others did not (e.g., Dawson & McGaugh, 1969; Elahi et al., 2020). Similarly, influential findings from studies with human participants showing reminder-dependent attenuation of fear memories (e.g., Kindt et al., 2009; Sevenster et al., 2012; Soeter & Kindt, 2011), or episodic memories (Walker et al., 2003), have failed to replicate (e.g., Bos et al., 2014; Hardwicke et al., 2016; Thome et al., 2016). Likewise, studies on post-reminder extinction, often also framed as a reconsolidation-based intervention, have yielded mixed results, with many of them showing fear memory attenuation in humans and rodents (e.g., Agren et al., 2012; Flavell et al., 2011; Liu et al., 2014; Monfils et al., 2009; Rao-Ruiz et al., 2011), but others failing to obtain such effects (e.g., Chalkia, Schroyens, et al., 2020a; Luyten & Beckers, 2017; Soeter & Kindt, 2011). Importantly, in many cases the attempted replication experiments adhered to the methodology of previously-published studies as closely as possible and yet they failed

to observe the expected outcome (Chalkia, Schroyens, et al., 2020a; Hardwicke, 2016; Luyten et al., 2021; Luyten & Beckers, 2017). Such failures to exactly replicate can be attributed to the occurrence of false-positive results in the original studies, the replication results being false negatives, or the absence of a clear understanding of the phenomenon. Replication failures can inspire a formal investigation of possible moderators to increase insight into the factors that may have led to those negative results and generally improve our understanding of when an effect can be observed, such as, for example, investigating the role of interindividual (Shumake et al., 2018) or subtle environmental (Schroyens, Bender, et al., 2019b) differences. Apart from these elusive occurrences of (exact) replication failures, we also identified the presence of problematic research practices within the field, such as flawed data processing and analysis in a highly influential publication (Chalkia, Van Oudenhove, & Beckers, 2020b) and publication bias (Schroyens et al., 2021).

Given the presence of several contradictory findings within the field, researchers should invest in maximizing credibility. In this regard, systematic and critical reviews of published results, as well as well-powered multi-site replication studies of previously published basic findings could help to gain more insight into whether reported results reflect true effects (i.e., assess *reliability*) and whether the effects hold over time, in different lab environments, populations, etc. (i.e., assess *generalizability*). In addition, it might be useful to examine the extent to which original conclusions hold when using different analysis strategies (i.e., assess *robustness*). As previously indicated, doing research in the absence of a well-specified theoretical framework entails a relatively high risk of obtaining false-positive results. If it turns out that (some of) the obtained effects are not reliable, robust, and/or have limited generalizability, it does not seem particularly useful to build a theoretical framework to explain those findings. As briefly illustrated below, several methodology-oriented tools can promote the credibility of the conclusions that are drawn from empirical research.

These tools often aim to do so by increasing research transparency, for example by making data and analysis scripts publicly available or preregistering hypotheses, methods, and planned analyses (i.e., archiving them in a public repository prior to data collection and under an embargo specified by the author) (Lakens, 2019; Nosek et al., 2018; Wagenmakers et al., 2012). *Preregistration* enhances researchers' ability to judge the credibility of published results and protects researchers from confirmation and hindsight bias. Integrating preregistration in the publication process in the format of a Registered Report moreover ensures that studies are published based on the soundness of the proposed research questions and quality of the methods regardless of the obtained outcome (Chambers, 2013). Research has shown that the use of preregistration and Registered Reports goes hand in hand with a decline in the percentage of published studies reporting statistically significant ("positive") results, possibly by decreasing the use of suboptimal research practices (Kaplan & Irvin, 2015; Scheel et al., 2021). Of note, preregistration does not guarantee that analysis plans and hypotheses are based on rational and justifiable decisions, and in itself cannot make up for bad theory.

Research transparency can be further increased by adopting additional method-oriented, as well as more theory-oriented approaches; first, by reporting the sensitivity of obtained results to arbitrary decisions made during data processing. Researchers typically choose from a range of several reasonable data processing options (e.g., which outliers to exclude, how to categorize or combine variables, etc.), and it has been proposed that insight in the robustness of statistical results can be improved by doing a "multiverse" analysis (Steegen et al., 2016) or "specification curve" analysis (Simonsohn et al., 2015), in which the results for all reasonable choices during data processing are reported. Second, transparency on a theory level could be enhanced if researchers indicate under which scenario(s) the proposed hypothesis would be disconfirmed, and whether that would challenge the underlying theory or whether changes to the theory should be made (Fried, 2021). Such specification would allow for a clearer judgment of the extent to which theory can be falsified by empirical testing (Lakens, 2019; Vanpaemel, 2019) and it may avoid the fact that predictions will almost certainly be confirmed by empirical observation.

Conclusion

Despite the existing replication issues and the use of suboptimal research practices, the amount of evidence in support of reminder-dependent amnestic effects is so widely available that we do not doubt the existence of the effect. Nevertheless, reminder-dependent amnesia does currently not live up to its clinical potential, and we hope that a more critical attitude towards potential underlying mechanisms will promote our knowledge of those amnestic effects. Therefore, we have highlighted some of the current theoretical issues and suggested possible solutions. Caution is required when inferring reconsolidation from behavioral results and when using reconsolidation theory to predict and account for such data. In addition, awareness should be raised regarding the lack of specificity in reconsolidation theory and the flexibility of boundary conditions. It is clear that these issues do not exclusively apply to the reconsolidation framework that we have appraised here; other fields in the behavioral sciences could benefit from such critical

analysis as well. Finally, we propose that every single step towards increasing transparency at a methodological and theoretical level would be beneficial for scientific progress, and, ultimately, for more fruitful translational efforts.

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