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Lose the fear and boost the everyday memory through memory destabilisation and reconsolidation

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ABSTRACT

This review starts with a brief description of key findings from Nader et al. (2000) which stimulate vibrant research of memory reconsolidation in the new millennium. It then zooms in to two aspects of the process that have important implications on whether a memory is susceptible to reconsolidation interference. First, memory strength contributes to a boundary condition on reconsolidation. The relevant receptor and circuit mechanisms are reviewed. Second, reactivation procedures affect memory destabilisation and memory susceptibility to reconsolidation interference. Recent null findings are briefly mentioned. Finally, it covers current discoveries of 'tagging along' reconsolidation to boost memory persistence. This review primarily focuses on evidence from fear conditioning paradigms, as interfering reconsolidation of fear memory paves ways for treating post-traumatic stress disorder (PTSD). Hippocampal-dependent spatial memories and reconsolidation are then discussed, as this approach provides crucial implications in boosting everyday memory persistence and insights on improving cognitive functions in aging.

1. From consolidation to reconsolidation

Numerous research findings have established the importance of encoding and consolidation in memory formation and persistence (Dudai, 2004; McGaugh, 2000). Related mechanisms underlying these processes are characterised and continue to be investigated (Johansen et al., 2011; Rodrigues et al., 2004). Learning driven by cue association with aversive outcomes such as a delivery of foot shocks provides a reliable model for memory research. These include auditory fear conditioning, contextual fear conditioning, and inhibitory avoidance.

The interference that is used to study consolidation can also be applied at memory reactivation. For example, earlier studies, that applied electroconvulsive shocks after learning, show impairment in memory consolidation (Gold et al., 1973; Haycock and McGaugh, 1973). When it was applied after cue-induced reactivation of a consolidated memory, memory impairment was also observed subsequently (Lewis et al., 1968; Misanin et al., 1968). Recognising the adverse effect of electroconvulsive shock, pharmacological approaches were then later used. For example, protein synthesis inhibition (Davis et al., 1976, 1980) was often used to induce amnesia.

By applying protein synthesis inhibition in the amygdala after fear memory reactivation, Nader et al. (2000) show an impairment in post-reactivation long-term memory (Fig. 1A). Several fundamental controls and confirmations were well designed to verify the selectivity or specificity of the reconsolidation process. First, a non-reactivation control shows that protein synthesis inhibition alone does not impair the memory. Second, when the protein synthesis inhibition is delayed by 6 h after reactivation, memory impairment is diminished. Third, post-reactivation short-term memory is tested and shown to be intact, suggesting the observed effect is selectively on reconsolidation. Fourth, reactivating the memory at 2 weeks after learning still leads to memory impairment by protein synthesis inhibition, confirming the effect at a different memory age (Nader et al., 2000).

Depending on the type of events that occur around reactivation, memory can be interfered (e.g. by blocking protein synthesis), strengthened (e.g. by retraining), updated (e.g. by extinction), or not modified. Topics around memory reconsolidation research include constraints or boundary conditions on reconsolidation (Wang et al., 2009a; Zhang et al., 2018), receptor or molecular mechanisms in reconsolidation (Tronson and Taylor, 2007) and in destabilisation (Finnie and Nader, 2012; Kida, 2019), implication in human cognition (Beckers and Kindt, 2017; Elsey et al., 2018; Schwabe et al., 2014),

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implication in treating people with PTSD (Pigeon et al., 2022; Raut et al., 2022), and so on. Constraints can come from several procedural aspects, such as training strength, memory age, how memory is reactivated, or reactivation vs. extinction trace dominance (Alberini et al., 2006; Duvarci and Nader, 2004; Duvarci et al., 2006; Eisenberg et al., 2003; Eisenberg and Dudai, 2004; Mamiya et al., 2009; Suzuki et al., 2004; Wang et al., 2009a). The next two sections will focus on constraints due to training strength and due to destabilisation that have significant implications in reconsolidation research.

2. Recent strong fear memory is insusceptible to reconsolidation interference

In auditory fear conditioning, a single or a small number of tone-shock pairing trials is typically sufficient to induce long-term memory in rodents. Whether the tone reactivation is non-reinforced, reinforced, or in the training context, the memory can be impaired through blocking protein synthesis in the amygdala (Duvarci and Nader, 2004; Duvarci et al., 2006; Nader et al., 2000). To understand if stronger auditory fear memory would also be susceptible to reconsolidation inference, rats receive 10 tone-shock pairings followed by reactivation and infusion of protein synthesis inhibitors in the amygdala. Strong fear memory is shown to be insusceptible to this type of interference whether the memory is reactivated via one non-reinforced trial, multiple non-reinforced trials, or one reinforced trial (Wang et al., 2009a). This fundamental effect of strong fear memory's insusceptibility to reconsolidation interference is reported by several researchers and across groups (Campbell et al., 2021; Haubrich et al., 2020; Holehonnur et al., 2016; Kwak et al., 2012; Pedraza et al., 2018; Sun et al., 2022).

At the circuit level, the hippocampus is involved in amygdala-dependent reconsolidation. Strong fear memory with a long reactivation delay (i.e., 60 days between training and reactivation) becomes susceptible to reconsolidation interference (Wang et al., 2009a). Memory with long retention is called remote memory and is associated with systems consolidation (Frankland and Bontempi, 2005; Wang et al., 2009b) and a complementary learning (McClelland and Goddard, 1996). It is postulated and shown that strong auditory fear memory in animals with an electrolytic hippocampus lesion can be weaken by reconsolidation interference (Wang et al., 2009a). Input from locus coeruleus to amygdala mediates emotional memory processes (Uematsu et al., 2017). Inhibiting the projection from locus coeruleus to amygdala (Fig. 1B) via chemogenetics renders the strong fear memory susceptible to reconsolidation interference (Haubrich et al., 2020).

At the receptor level, the presence of GluN2B subunits of NMDA receptors is associated with memory destabilisation function. Down-regulation of these subunits after strong fear conditioning prevents memory destabilisation. Zinebi et al. (2003) use electrophysiology to characterise the NMDA-dependent potentiation and western blot to measure protein levels. They show that strong fear conditioning leads to the reduction of NMDA receptor-mediated excitatory postsynaptic currents in paired-pulse facilitation, a shift in dose-dependent curve in NMDA-induced currents, and a decrease in GluN2B and GluN2A, but not

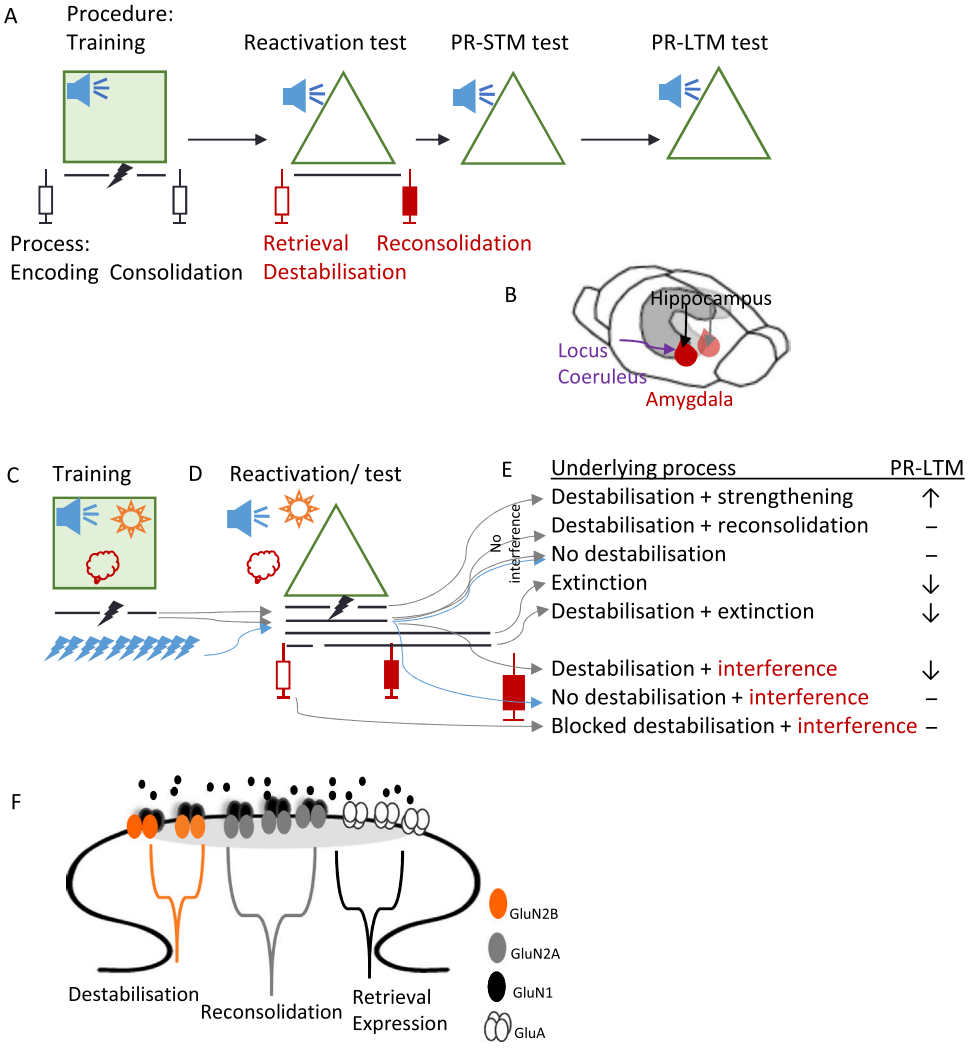

Fig. 1. Summary of key processes (A), circuit mechanisms (B), procedural factors (C,D), memory consequences (E), and receptor mechanisms (F) in memory destabilisation and reconsolidation. (A) Schematic procedures for auditory fear conditioning, post-reactivation short- or long-term tests (PRSTM/ LTM) and process being probed by intervention before/ after training or reactivation. (B) Inputs from the hippocampus and locus coeruleus to amygdala have been shown involved in destabilisation of strong fear memory. (C) Training strength (a small or large number of tone-shock pairings) and stimuli (tone, visual cues, olfactory cues, textures, geometric shapes of the apparatus) may influence the content and strength of the memory. (D) Reactivation procedures (a reinforced trial, a non-reinforced brief trial, along trial, a brief followed by a long trial, indicated by lines under the triangle apparatus), stimuli (tone, visual, olfactory cues), and the timing and type of intervention (blockage of the destabilisation, indicated by an open syringe; interference of reconsolidation, indicated by a solid syringe) can, in conjunction with training in (C), influence what processes take place and the consequence of the memory in (E). (F) GluN2B-NMDA, GluN2A, and GluA receptors have been implicated in fear memory destabilisation, reconsolidation, and expression.

in GluN1 protein expression. The decrease of GluN2B and intact GluN1 are reproduced in other studies (Holehonnur et al., 2016; Wang et al., 2009a). With testing through multiple antibodies against GluN2B and optimising the incubation for immunohistochemistry, reduction of GluN2B+ cells after strong fear conditioning is observed in both lateral and basal amygdala (Wang et al., 2009a). An increased GluN2A/2B ratio is also reported in strong fear conditioning (Holehonnur et al., 2016; Wang et al., 2009a).

A pattern is observed with GluN2B downregulation in conditions where the strong fear memory is insusceptible to reconsolidation interference, and no downregulation when the memory is susceptible to reconsolidation interference. For causal evidence, manipulation of the GluN2A/2B ratio is shown to affect whether the fear memory is susceptible to reconsolidation interference. In a Tet-off system where off doxycycline enables transgene expression of GFP-GluN2A, reduction of GluN2B/PSD95, an increase in GluN2A/PSD95, and an increase in GluN2A/GluN2B in the lateral and basal amygdala are observed. After fear conditioning with 3 tone-shock pairings, the memory that is normally susceptible to reconsolidation interference becomes insusceptible to it when the GluN2A/GluN2B ratio in the amygdala is increased through induced GluN2A expression after consolidation (Holehonnur et al., 2016). These studies together suggest a crucial role of GluN2B-containing NMDA receptors in enabling the memory's susceptibility to reconsolidation interference, a process called memory destabilisation.

A recent study suggests that compound behavioural procedures combining pharmacological treatment can weaken strong fear memory, which is, however, not purely due to reconsolidation interference. After 10 tone-shock pairings, animals receive 8 days of 10 tone trials per day without shocks (Campbell et al., 2021). This leads to a reduction of freezing, which reflects extinction learning that inhibits the original trace (Bouton et al., 2021). This temporary inhibition is evident by moderate return of freezing during the tone replay in a novel context, called renewal. Post-renewal, systemic injection of GABA-A receptor agonist, midazolam, reduces this moderate level of freezing on the next day. As at the stage of renewal, the original fear memory trace, the extinction memory trace, and the potential trace of new learning of the tone-novel context are likely to co-exist or compete. One may not be able to conclude that it is the strong fear memory that now undergoes reconsolidation. This is because, first, tone reactivation with midazolam injection, compared with tone reactivation and vehicle injection, on the day after strong conditioning does not differentially affect subsequent freezing in extinction or retesting in a third context (Campbell et al., 2021). Second, the interaction between training strength and reactivation duration can determine what process is affected by interference or pharmacological injection (Eisenberg et al., 2003; Mamiya et al., 2009; Suzuki et al., 2004).

The strength of memory sets a constraint on whether memory can be affected by reconsolidation interference. It is important to develop a system to comprehensively describe memory strength objectively. Moving forward, the number of conditioning trials, intensity of unconditioned stimuli, the conditioned response level at memory reactivation, at post-reactivation memory tests, and the extinction tests should be provided (Fig. 1C-D) to form indices to support if a boundary condition, due to memory strength, is met and is contributing to the insusceptibility to reconsolidation interference (Fig. 1E). This is not trivial as similar levels of freezing at reactivation may not differentiate the memory strength, which needs to be inferred from training parameters and how extensive the extinction is needed to cause reduction in conditioned responses (Grady et al., 2016; Wang et al., 2009a). The implication in human cognition is that some training protocols may lead to strong memory in some participants and that their memory is resistant to reconsolidation interference. Different components of compound memory in people with PTSD may have different memory strength, which may contribute to the susceptibility to reconsolidation interference. It is also not trivial to measure memory strength in humans, which is likely affected by factors beyond those involved in lab animal research. These include individuals' expectation, instructions received, and past experiences.

3. Destabilisation enables memory susceptibility to reconsolidation interference

It has been proposed that for the memory to be disrupted by reconsolidation interference or to be updated, memory reactivation has to engage a destabilisation process to render memory susceptible to subsequent interventions (Finnie and Nader, 2012; Kida, 2020; Lee et al., 2012). At the behavioural level, studies show that mismatch between reinforced training and non-reinforced reactivation is a key factor in enabling destabilisation (Osan et al., 2011; Pedreira et al., 2004). This is however not the case for auditory fear memory (Duvarci and Nader, 2004; Popik et al., 2020). Prediction errors between learning and reactivation is used to describe when reconsolidation impairment is seen (Gotthard and Gura, 2018; Gotthard et al., 2018; Sevenster et al., 2013) but recent studies suggest this may not always be seen (Cahill et al., 2019; Junjiao et al., 2019; Stemerding et al., 2022).

At the circuit level, the locus coeruleus-amygdala projection is involved in strong auditory fear destabilisation as mentioned above (Haubrich et al., 2020). Inactivating nucleus reuniens will prevent contextual fear memory from reconsolidation interference by protein synthesis in this region or systemic clonidine injection (Troyner and Bertoglio, 2020). Activating the projection from the nucleus tractus solitarius to the amygdala before a reactivation trial with the conditioned stimulus only enables memory impairment by protein synthesis inhibition in the amygdala in a morphine self-administration task (Zheng et al., 2022).

At the receptor level, intra-amygdala infusion of a NMDA receptor antagonist, ifenprodil that targets GluN1 and GluN2B receptors, prevents the reconsolidation impairment of auditory fear memory caused by post-reactivation protein synthesis inhibition in the same brain region (Ben Mamou et al., 2006). This is supported by a study further showing selective roles of GluN2B-NMDA receptors in destabilisation and GluN2A-NMDA receptors in reconsolidation (Milton et al., 2013) and a study using ifenprodil in preventing appetitive reconsolidation interference of contextual fear memory (Ferrer Monti et al., 2016). In an object recognition paradigm, pre-reactivation/retraining infusion of GluN2B-NMDA receptor antagonist, Ro25–6981, also prevents protein synthesis inhibition in perirhinal cortex from interfering recent memory reconsolidation (Wideman et al., 2020). GluN2B-NMDA receptors in the CA1 of dorsal hippocampus are also involved in destabilisation of extinction memory in inhibitory avoidance (Radiske et al., 2021a). These together support the role of GluN2B-containing NMDA receptors in memory destabilisation (Fig. 1F).

In a reconsolidation-extinction paradigm, blocking AMPA receptor endocytosis via injection of TAT-GluA2$_{3Y}$ in the dorsal hippocampus, prevents the updating of the contextual fear memory from extinction and enables the spontaneous recovery of fear (Rao-Ruiz et al., 2011). Intra-amygdala infusion of GluA2$_{3Y}$ also prevents destabilisation of auditory fear memory (Hong et al., 2013). Pre-reactivation infusion of AMPA receptor antagonists in the amygdala however impairs memory expression in auditory fear conditioning (Milton et al., 2013). Intra-amygdala blockade of calcium-permeable AMPA receptors that lack GluA2 before tests impairs contextual and auditory fear memory expression (Torquatto et al., 2019). Synaptic removal of calcium-permeable AMPA receptors in the amygdala is shown in ex vivo recoding after reconsolidation-extinction and systemic mGluR1 inhibition prevents the less renewal or spontaneous recovery after reconsolidation-extinction updating (Clem and Huganir, 2010). Voltage-gated calcium channels and cannabinoid receptor type 1 are also shown to involve in destabilisation of contextual fear memory (Suzuki et al., 2008). Using object tasks, M1 muscarinic cholinergic receptors in the perirhinal cortex is involved in destabilisation of object

recognition, and in the dorsal hippocampus in object location recognition (Huff et al., 2022; Jardine et al., 2020). Dopaminergic D1/Dd5 receptors in the hippocampus are involved in destabilisation of object recognition (Gonzalez et al., 2021).

At the molecular level, inhibiting protein degradation in the hippocampus or in the nucleus reuniens prevents reconsolidation interference of contextual fear memory (Lee, 2008; S.H. Lee et al., 2008; Troyner and Bertoglio, 2020). In a reactivation-relearning paradigm, inhibiting protein degradation can prevent the strengthening of contextual fear memory (Lee, 2008). CaMKII is suggested to be upstream of protein degradation and inhibiting CaMKII in the amygdala, albeit post reactivation, prevents memory impairment by protein synthesis inhibition (Jarome et al., 2016). ProBDNF pathway in the prelimic cortex is implicated in memory destabilisation in juvenile rats but its influence on reconsolidation is not entirely ruled out (Sun et al., 2022).

While advancement in understanding above mechanisms, null results on reconsolidation interference through systemic injections of beta adrenergic blockers propranolol in rats (Luyten et al., 2021) or in mice (Cox et al., 2022), or of midazolam or cycloheximide in rats (Schroyens et al., 2017) have been reported. Differentiating whether the drug does not work, the memory does not destabilise upon reactivation, or the drug does not work on reconsolidation will be crucial. Adding positive controls to show the drug's effect can rule out issues with the drug application. Using a more established approach to interfere reconsolidation (e.g., intra-cranial inhibition of protein synthesis in the brain regions required for the task) can rule out issues with the behavioural procedures and verify if destabilisation occurs. One recent approach uses ex vivo molecular readout to show if destabilisation is engaged (Rotondo et al., 2022). Other factors of considerations are the past experiences of the context which affect subsequent learning and memory destabilisation (Radiske et al., 2017, 2021b), the holding and transportation context, learning of configural or elemental cues (Goldfarb et al., 2021), and memory reactivation of compound or elemental cues (Drame et al., 2020; Zheng et al., 2022). A schematic model based on the type of training, memory strength, methods of reactivation, and the consequence of reconsolidation interference for water maze-related spatial memory is drawn previously (Wang and Morris, 2010) and a simple schematic model for fear memory is provided in Fig. 1C-E.

Mixed results are also seen in human research with reactivation-extinction, or reactivation-extinction-propranolol in healthy adults, or with reactivation-propranolol in reducing symptoms in people with PTSD (e.g. Chalkia et al., 2020; Junjiao et al., 2019; Stemerding et al., 2022). Replies to the challenges and ways to move forward have been proposed (Beckers and Kindt, 2017; Elsey et al., 2018; Monfils and Holmes, 2018; Schiller et al., 2020). Meta-analyses can provide a comprehensive view of the overall effect across studies. For example, a recent analysis shows promising effects of reconsolidation-propranolol in reducing recall of aversive memory in healthy participants and in reducing symptoms in people with PTSD, substance dependence, or specific phobia. The caveats are the significant heterogeneity across studies and publication bias (Pigeon et al., 2022). Another meta-analysis with fewer studies shows no significant improvement on symptoms while there is reduction in heart rates. The limitations are varied dosages and heterogeneity across studies (Raut et al., 2022). Human memory research allows the collection of enriched, multi-faceted measurements. It is possible to develop a 'destabilisation index' that combines measurements from physiological or behavioural responses before and after training, in early and in late reactivation, the rate of extinction, subject's rating of prediction, reappraisal, stress, and traits (Bach and Melinscak, 2020; Constantinou et al., 2021; Elsey et al., 2018; Kitamura et al., 2022). With increasing amounts of health information, genetic information, functional brain imaging, and molecular brain imaging data from biobanks, models that combine these factors and the 'destabilisation index' will enable precision medicine in cognition.

4. Peri-reactivation novelty facilitates memory persistence

An important function of reactivation and reconsolidation is memory updating (Lee et al., 2017). Our daily memory involves remembering where things are, such as where the keys are last seen or where the car or bike is parked. Reactivation of this type of memory can open a time window to retain relevance of the memory and prevent its fading. A rodent model is developed to mimic our daily experience of remembering particular locations in spatial navigation (Bast et al., 2005). It is shown that a weak encoding in this appetitive, delayed matching-to-place task leads to short-term memory, while novelty around weak encoding enables the memory to persist longer (Wang and Morris, 2010). Peri-learning events in modulating memory persistence is called behavioural tagging and is developed from the synaptic tagging and capture hypothesis (Moncada et al., 2015; Wang and Morris, 2010). The cellular mechanism for behavioural tagging is characterised (Gros et al., 2022; Nomoto et al., 2016).

Recent studies further show that novelty introduced around memory reactivation also improves memory persistence. Using the same place task, exploration in a novel box before or after a reactivation of the previously encoded location can improve long-term memory (Gros and Wang, 2018; Wang, 2018). By changing the reactivation location or by inhibiting protein synthesis in the hippocampus, it is verified that destabilisation and reconsolidation occurs in this task (Wang, 2018). Reconsolidation of the place memory is however not susceptible to the interference of hippocampal immediate early genes, zif268, as seen in other tasks (Gonzalez et al., 2019; Lee et al., 2004).

In addition to facilitating memory persistence, novelty is also shown to rescue memory impairment due to interference of consolidation or reconsolidation. In the same place task or in contextual fear conditioning, exploration in a novel box can prevent memory impairment caused by reconsolidation interference (Wang, 2018). This effect is also supported by inhibitory avoidance studies. Rabinovich Orlandi et al. (2020) show that exploration in an open field within a time window before or after reactivation of the avoidance memory, can reverse impairment caused by post-reactivation, intra-hippocampal infusion of protein synthesis inhibitor emetine or MEK/ERK1/2 Inhibitor U0126. Reconsolidation impairment led by PKA inhibitor rp-cAMP however is not rescued by pre-reactivation open field exploration. A similar pattern of results is seen with object recognition memory in the same study. It is suggested that reactivation would (re-)engage the tagging mechanism that is dependent on PKA.

Using memory reconsolidation as an event, Cassini et al. (2013) examine if it can enable memory persistence of a second task of interest. They show that weak training of object location alone does not lead to long-term memory. When reactivation of a contextual fear memory occurs around the weak training of object location, the object location memory can last for a long term. This effect is blocked by protein synthesis inhibition in the hippocampus when applied at contextual fear memory.

The concept of reconsolidation also helps to elucidate the process in spaced learning. Correa et al. (2022) use an object location task and show that strong training on day 1 with weak training on day 2, leads to memory persistence for 7 days. In a 3-day protocol, day 1 strong training alone leads to memory on day 3, and day 1 strong training with day 2 weak training does not improve it further. Intra-hippocampal inhibition of protein synthesis or of mammalian target of rapamycin complex 1, after weak training on day 2 does not interrupt the memory. Either one of these infusions given before weak training interrupts memory persistence for 7 days. It is suggested that in the latter case, the second weak trial reactivates the memory trace and renders it susceptible to reconsolidation interference. Exploration in an open field after weak training-emetine interference can reverse the memory impairment (Correa et al., 2022).

Together, this evidence would suggest that (1) novelty, likely through production of plasticity-related proteins, enables decaying

memory to last or reverses memory impairment due to protein synthesis inhibition, and (2) reactivation is likely to engage or re-engage the tagging mechanism, and if this is blocked (e.g., by PKA inhibition), novelty cannot enable the memory persistence. It is to be noted that 'strong training in the context of behavioural tagging' refers to training that leads to observation of long-term memory, typically at 24 h after training (Moncada et al., 2015; Wang and Morris, 2010). 'Strong training in the context of reconsolidation' is defined by more training trials beyond what is sufficient for forming long-term memory. It is also associated with more extinction trials that are needed to reduce condition responses (Wang et al., 2009a), a significant change at GluN2B receptor expression (Holehonnur et al., 2016; Wang et al., 2009b; Zinebi et al., 2003), and insusceptibility to reconsolidation interference (Haubrich et al., 2020; Holehonnur et al., 2016; Wang et al., 2009a).

5. A personal reflection

It was a privilege to join Prof Karim Nader's group and engage in reconsolidation research – an immensely energetic researcher and in a fast-moving field. The story behind the discovery of GluN2B down-regulation after strong fear conditioning is that we had found the strong fear memory insusceptibility to reconsolidation interference, but the molecular mechanism was unclear. One day Karim showed us the Zinebi et al. paper and we realised the NMDA changes in that paper reflected a strong training effect. After numerous attempts with different antibodies, titrations, washing buffers, and incubation durations, good immunostaining was achieved. It was a − 20 °C snowy evening when I ran to Boul. de Maisonneuve to find Karim busy hosting a speaker. We then looked at the amygdala-GluN2B image like it was an art masterpiece. This story will mean different things to different people. Is the memory of the story holistic, configural, or elemental? Will it undergo destabilisation, reconsolidation, interference, strengthening, or updating? We will see.

6. Conclusions

Modification or manipulation of memory through reconsolidation has been widely demonstrated and through reconsolidation research, we gain tremendous amount of knowledge on brain functions. It is important to recognise scenarios when a change of the memory observation is not apparent. This includes strong fear memory and memory that does not destabilise. Moving forward, we need to develop indices and methods to better describe the complexity of scenarios in memory reconsolidation (Fig. 1C). Drawing an analogy from precision medicine in Psychiatry (Menke, 2018; Manchia et al., 2020), information from past experiences, training histories, reactivation procedures, stress levels, diets, lifestyles, genetics, and so on can be used to optimise treatments for memory-related symptoms or disorders. Finally, 'tagging long' memory reactivation and reconsolidation paves a new way for improving memory persistence.

Data Availability

No data was used for the research described in the article.

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