Modification of Human Adverse Memories: Evidence from Memory Reconsolidation

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Abstract

After consolidated long-term memories are retrieved, they enter a labile period during which the memories can be updated, strengthened, weakened, or even erased; this process is called reconsolidation. Studies on the reconsolidation of aversive memories in humans have revealed that after memory activation, oral administration of propranolol or extinction training can weaken or erase aversive emotional memories, a process that involves the participation of brain regions such as the amygdala, hippocampus, and prefrontal cortex, as well as the regulation of neural circuits formed by these structures. Currently, in clinical practice, the principle of reconsolidation is utilized to modify aversive memories through pharmacological treatment, behavioral intervention, or non-invasive brain stimulation methods. However, due to the complex formation process and influence of multiple factors, future research should strive to simulate the complex environments in which aversive memories form in clinical settings, thoroughly investigate the "boundary conditions" of reconsolidation, and promote the translation of laboratory research to clinical applications.

Full Text

Modulating Maladaptive Human Memory: Evidence from Reconsolidation

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Abstract

When consolidated long-term memories are retrieved, they enter a labile state during which they can be updated, strengthened, weakened, or even erased —a process known as reconsolidation. Research on the reconsolidation of maladaptive human memory has revealed that oral administration of propranolol or extinction training following memory activation can attenuate or eliminate aversive emotional memories. This process involves the participation of brain regions such as the amygdala, hippocampus, and prefrontal cortex, as well as the regulation of neural circuits they comprise. Currently, clinical interventions based on reconsolidation principles can alter maladaptive memories through pharmacological treatment, behavioral intervention, or non-invasive brain stimulation. However, due to the complex formation processes and multiple influencing factors, future research should strive to simulate the complex environments in which human maladaptive memories form in clinical settings, thoroughly investigate the "boundary conditions" of reconsolidation, and promote the translation of laboratory findings to clinical applications.

Keywords: maladaptive human memory; reconsolidation; clinical intervention; boundary conditions

1. Introduction

Maladaptive human memory refers to negative emotional memories formed after traumatic experiences, characterized by intense negative emotional experiences that persist over time [?, ?]. Such memories represent a common feature of many psychiatric disorders. For instance, post-traumatic stress disorder (PTSD) involves the formation of maladaptive emotional memories following severe traumatic events [?, ?], and these aversive memories constitute a key pathological mechanism in the subsequent development of PTSD. Similarly, maladaptive memories are prevalent in other psychiatric conditions. Patients with phobias and obsessive-compulsive disorder exhibit memory biases toward threat-related information [?, ?, ?]. Therefore, how to weaken or even erase these exceptionally robust maladaptive memories represents a critical challenge.

For over a century, it was believed that newly acquired memories undergo a brief dynamic unstable period before being consolidated into a stable state. Once consolidated, memories were considered permanent and resistant to disruption [?, ?]. However, this traditional memory consolidation theory has faced significant challenges. Evidence indicates that retrieving a consolidated memory can return it from a stable to an unstable state, a process termed memory reconsolidation [?, ?, ?]. During reconsolidation, memories can be updated, strengthened, weakened, or erased, thus providing a modifiable window for previously stable memories [?, ?, ?, ?, ?, ?, ?, ?, ?].

To date, interventions targeting negative emotional memory reconsolidation have been extensively studied in animal models, with in-depth investigations of the neural circuits regulating negative emotional memory reconsolidation

[?, ?, ?, ?, ?, ?], key nuclei [?, ?, ?, ?, ?, ?, ?, ?, ?], and underlying cellular and molecular mechanisms [?, ?, ?, ?, ?, ?, ?, ?, ?, ?]. In recent years, numerous scholars have extended these theoretical findings to research on modifying maladaptive human memory, conducting substantial theoretical and preliminary practical investigations. This paper first reviews and summarizes theoretical research on intervening in human maladaptive memory based on reconsolidation principles, elaborates on the neural regulatory mechanisms underlying human maladaptive memory reconsolidation, and then evaluates the clinical application of reconsolidation theory in treating psychiatric disorders from three perspectives: pharmacological intervention, behavioral extinction, and non-invasive brain stimulation. Finally, we identify current problems in research on intervening in human maladaptive memory using reconsolidation principles and propose future research directions.

2. Theoretical Research on Modifying Maladaptive Human Memory Based on Reconsolidation Principles

Evidence from animal experiments demonstrates that reactivated negative emotional memories can be modified [?, ?, ?, ?]. Similarly, researchers have explored the modification of human maladaptive memory using reconsolidation principles. Current theoretical research on human maladaptive memory primarily focuses on two memory types: fear memory and negative episodic memory. Since drugs used to block reconsolidation in animal experiments pose potential harm to humans, propranolol—a non-toxic beta-blocker—has been employed as a pharmacological intervention in human studies. However, an increasing number of studies have 倾向于 explored non-invasive methods such as retrieval-extinction behavioral therapy or magnetic stimulation to modify maladaptive memories.

2.1 Human Fear Memory Reconsolidation Research

Kindt, Soeter, and Vervliet (2009) first investigated the role of the -adrenergic receptor blocker propranolol in human fear memory reconsolidation. Their study found that healthy participants who underwent fear conditioning and received propranolol before memory retrieval showed disrupted fear memory reconsolidation, inhibiting subsequent fear memory expression and retention. To exclude the possibility that propranolol affected the memory retrieval phase itself and to confirm its specific effect on the reconsolidation stage, the researchers administered propranolol immediately after fear memory retrieval. Testing 24 hours later revealed significant suppression of fear memory expression [?, ?, ?]. Further investigation by Kindt and Soeter (2018) examined the effective time window for oral propranolol to disrupt fear memory reconsolidation. Results indicated that administering propranolol one hour before or after memory retrieval disrupted the reconsolidation process and blocked subsequent fear memory expression. In contrast, administering nadolol three hours before retrieval or propranolol two hours after retrieval had no effect on fear memory reconsolidation, suggesting that effective intervention occurs within a brief temporal window. Similarly,

research has reported that administering cortisol after memory retrieval can also disrupt fear memory reconsolidation and inhibit fear memory expression [?, ?, ?, ?, ?, ?]. These findings suggest that pharmacological disruption of reconsolidation requires careful timing to ensure that the drug' s peak effect coincides with the effective intervention window. In subsequent fear memory testing, oral propranolol indeed reduced participants' fear responses [?, ?], such as diminished startle reflexes to fear stimuli. However, participants' subjective fear expectancy and physiological measures like skin conductance remained unchanged [?, ?], indicating that the associative memory trace between the conditioned stimulus (CS) and unconditioned stimulus (US) may not have been completely eliminated. Soeter and Kindt (2010) confirmed this dissociation, though no comprehensive study has yet investigated the underlying reasons for this phenomenon or the differences in its internal regulatory mechanisms. Future research should explore core measurement indicators that can effectively assess fear memory elimination and predict its recurrence.

An alternative approach to eliminating fear memory involves extinction training during the reconsolidation phase following memory activation. When extinction training was conducted 10 minutes after fear memory activation, it disrupted fear memory reconsolidation and inhibited subsequent fear memory expression, with this inhibitory effect lasting at least one year [?, ?, ?]. In contrast, extinction training conducted six hours after fear memory activation had no effect on fear memory expression [?, ?]. Similarly, extinction training within the reconsolidation window can also inhibit the recurrence of fear memories triggered by auditory aversive stimuli [?, ?]. However, successful extinction of maladaptive memories within the reconsolidation window depends on effectively activating the established memory, though the optimal method for memory activation remains controversial. Most studies have activated established fear memories by presenting the CS once [?, ?] or multiple times [?, ?]. However, some researchers have found that extinction after a single CS presentation does not suppress fear memory expression [?, ?, ?, ?, ?, ?, ?]. Sevenster, Beckers, and Kindt (2012) supported this view and proposed that merely presenting a learned conditioned stimulus (fear-related cue) is insufficient to effectively activate fear memory and induce reconsolidation. Instead, presenting stimuli that differ from those used during the learning phase during memory retrieval is necessary to effectively activate established fear memories [?, ?, ?, ?, ?]. These inconsistencies may stem from differences in experimental procedures, including variations in the unconditioned stimulus (e.g., aversive auditory stimuli in Oyarzun et al. vs. electric shock in Schiller et al.), differences in reinforcement protocols or trial numbers during fear memory acquisition (e.g., 50% vs. 80% CS-US pairing probability, which directly affects memory strength), differences in stimuli or presentation methods during memory activation (e.g., selective presentation of a single CS when multiple CSs were paired with the same US, and varying numbers of CS presentations), and differences in fear memory assessment measures (e.g., skin conductance alone vs. startle reflex vs. combined startle reflex and US expectancy measures). Therefore, as a non-invasive and safe method for clinical

application, the efficacy of extinction training within the reconsolidation window and the boundary conditions for reconsolidation, such as effective methods for memory activation, require further clarification.

2.2 Human Negative Episodic Memory Reconsolidation Research

Whether established long-term negative episodic memories can be modified and how to modify them have only recently been investigated. For example, administering propranolol before activating memories associated with negative emotional images weakened participants' subjective judgments of the memory trace strength for those images [**?**, **?**, **?**, **?**] and reduced recognition rates for negative emotional images in a recognition test conducted 24 hours after memory retrieval. In addition to pharmacological intervention, Chan and LaPaglia (2013) proposed using a retrieval-relearning behavioral intervention to weaken maladaptive memories. Participants first watched a film depicting a terrorist attack to form negative episodic memories. During subsequent memory retrieval, memories were activated by having participants recall details of the film, after which they immediately learned new information. Testing 24 hours after retrieval demonstrated disruption of the original episodic memory reconsolidation process, with the inhibitory effect on the original memory lasting at least 48 hours. Recent research has also shown that administering electroconvulsive therapy (ECT) after memory retrieval can disrupt negative episodic memory reconsolidation [**?**, **?**]. Thus, retrieval-relearning behavioral intervention techniques and non-invasive physical stimulation—ECT—provide new avenues for clinically intervening in negative emotional memories using non-invasive methods.

3. Neural Mechanisms of Maladaptive Human Memory Reconsolidation

While the neurobiological mechanisms of negative emotional memory reconsolidation have been extensively investigated in animal studies, research on the neural mechanisms of human maladaptive memory reconsolidation has been limited by methodological constraints and has primarily relied on brain imaging evidence. In recent years, combining non-invasive brain stimulation with neuroimaging to explore the neural mechanisms of memory reconsolidation has garnered significant attention. Current laboratory research has focused on the specific brain regions activated during maladaptive human memory retrieval and the neural circuit mechanisms constituted by these activated regions.

Schwabe, Nader, Wolf, Beaudry, and Pruessner (2012) conducted functional magnetic resonance imaging (fMRI) during both the retrieval (activation) and recognition phases of negative emotional picture memories to investigate the neural mechanisms underlying propranolol-induced disruption of negative emotional memory expression. Results indicated that during negative emotional memory retrieval, the hippocampus and amygdala were significantly activated, with no

significant differences in brain activity between propranolol and placebo groups, suggesting that propranolol itself may not affect memory trace activation. During the recognition phase, when comparing correct versus incorrect recognition of negative emotional pictures, no significant differences in brain activation were observed between propranolol and placebo groups under non-activated memory conditions. However, under activated memory conditions, the left amygdala and bilateral hippocampus showed significantly greater activation in the propranolol group compared to the placebo group, demonstrating that correct recognition of negative emotional pictures requires hippocampal and amygdala involvement and suggesting that brain regions active during memory activation may be relevant for subsequent memory retrieval. Similarly, neuroimaging evidence in fear memory reconsolidation research has revealed the central regulatory role of the amygdala. Studies show that compared to extinction training conducted six hours after memory activation, extinction training performed 10 minutes after activation reduces amygdala activity during fear memory testing 24 hours later [**?**, **?**, **?**, **?**], with amygdala activation positively correlating with subsequent fear memory recurrence [**?**, **?**, **?**].

At the neural circuit level, Feng, Zheng, and Feng (2015) proposed that during fear memory activation, the dorsal anterior cingulate cortex (dACC) and ventromedial prefrontal cortex (vmPFC) show significantly enhanced activity, with increased functional connectivity between the amygdala and vmPFC. If fear memory is extinguished after activation, vmPFC activity decreases and vmPFC-amygdala functional connectivity weakens [**?**, **?**, **?**, **?**, **?**, **?**], suggesting that suppressing vmPFC activity and the amygdala-vmPFC circuit may be key mechanisms for completely preventing fear memory recurrence. Additionally, when transcranial direct current stimulation (tDCS) was applied to the right dorsolateral prefrontal cortex (DLPFC)—a region involved in negative emotion processing [**?**, **?**]—after memory activation, fear memory was significantly enhanced in the stimulation group compared to the control group during testing 24 hours later [**?**, **?**]. These findings suggest that different prefrontal regions and their neural circuits with the amygdala may play crucial roles in fear memory processing.

Current neuroscience research has clearly identified brain regions activated after human maladaptive memory retrieval, including the dACC, vmPFC, DLPFC, and amygdala. However, the functional connectivity characteristics among these activated nuclei and their regulatory roles in human maladaptive memory reconsolidation processing remain unclear. Therefore, future research should further elucidate the neural circuit mechanisms regulating human maladaptive memory reconsolidation processing at the systems level.

4. Clinical Interventions for Maladaptive Human Memory Based on Reconsolidation Principles

Based on theoretical laboratory research on human maladaptive memory, investigators have conducted preclinical explorations of interventions from three per-

spectives: pharmacological treatment, behavioral extinction, and non-invasive brain stimulation. These studies have achieved substantial progress, particularly regarding non-invasive brain stimulation targeting specific brain regions and neural circuits, providing new insights for clinical intervention of human maladaptive memory.

4.1 Pharmacological Treatment

Modifying established emotional memories holds significant importance for many psychiatric disorders, including anxiety disorders, PTSD, and drug addiction. In PTSD, the persistent presence of traumatic memories results largely from excessive processing and consolidation of traumatic events, with stress hormones such as glucocorticoids and norepinephrine playing crucial roles [**?**, **?**]. Research indicates that these hormones contribute to the formation of abnormally robust trauma-related memories [**?**, **?**, **?**]. Therefore, a key intervention strategy is blocking these hormones' effects when stress occurs. Existing studies demonstrate this approach' s effectiveness [**?**, **?**, **?**, **?**]. However, administering consolidation blockers at the onset of trauma is impractical, making pharmacological intervention during reconsolidation particularly important for eliminating traumatic memories. After activation, traumatic memories become labile and susceptible to interference, providing a therapeutic opportunity. If traumatic memories can enter this unstable state after activation, interference during this phase could treat strong, persistent traumatic memories. For example, PTSD patients describe personal traumatic experiences to activate established traumatic memories before receiving propranolol or placebo. One week later, all patients describe their traumatic experiences again. Results show that when recounting traumatic events, PTSD patients who received propranolol exhibit weaker psychophysiological responses (heart rate, skin conductance) compared to those who received placebo [**?**, **?**]. Although these traumatic events occurred long ago and the study lacked a control group (non-retrieval group), the findings nonetheless suggest that post-retrieval intervention represents a powerful method for treating PTSD.

4.2 Behavioral Intervention

The behavioral intervention method based on reconsolidation principles is the retrieval-extinction paradigm, in which an established maladaptive memory is retrieved (activated) and then extinguished through presentation of memory-related cues (conditioned stimulus, CS) without the unconditioned stimulus (US) during the reconsolidation window, thereby inhibiting subsequent memory recurrence [**?**, **?**]. Current research suggests that the reconsolidation window lasts up to six hours after memory retrieval [**?**, **?**, **?**]. During this window, previously stored memories re-enter a labile state, and the new memory association (CS-no US) learned during extinction training integrates into the previously stored memory trace (CS-US), thereby disrupting the original maladaptive memory trace [**?**, **?**]. Thus, extinction training within the reconsolidation window can

effectively weaken or even erase human maladaptive memories. Shiban, Brutting, Pauli, and Muhlberger (2015) demonstrated that activating spider-phobic patients' fear memories through relevant cues followed by extinction training inhibited subsequent fear recurrence. Similarly, Maples-Keller et al. (2017) explored retrieval-extinction paradigm intervention for fear of flying (FoF), finding that patients' clinical symptoms (heart rate, skin conductance) significantly decreased after behavioral intervention, with this inhibitory effect lasting at least three months. However, both Shiban (2015) and Maples-Keller (2017) found that activating or not activating maladaptive memories before extinction (through presentation of memory-related cues) could both inhibit subsequent memory recurrence, with no significant difference in the degree of inhibition between these conditions. Currently, evidence for using the retrieval-extinction paradigm to intervene in maladaptive memories in patient populations remains limited. Nevertheless, research on heroin addicts has shown that presenting heroin-related cues to activate drug-associated memories followed by extinction training reduces drug craving, with a significant difference in subsequent craving between memory activation and non-activation groups [**?**, **?**]. Therefore, while the retrieval-extinction paradigm based on reconsolidation theory represents a theoretically non-invasive method for weakening or erasing maladaptive memories, its efficacy in clinical patient populations requires further investigation.

4.3 Non-invasive Brain Stimulation (TMS/tDCS)

In recent years, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have emerged as promising non-invasive therapies for intervening in human memory [**?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**]. These non-invasive techniques combine individual structural MRI data with frameless brain localization systems to target specific regions, modulating behavior by stimulating particular cortical areas based on their correspondence with human memory functions [**?**, **?**]. Due to their sustained effects, TMS and tDCS can also treat psychiatric disorders [**?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**]. Studies have found that combining traumatic event exposure with repeated TMS (rTMS) stimulation of the medial prefrontal cortex can alleviate PTSD symptoms [**?**, **?**]. Similarly, nicotine withdrawal patients who received multiple daily sessions of deep rTMS to the lateral prefrontal cortex and insula after smoking-related cue exposure showed reduced smoking frequency, with treatment success rates reaching 44% and 33% maintaining abstinence at six-month follow-up [**?**, **?**]. Furthermore, rTMS can be applied not only to single brain regions but also to investigate functional connectivity between regions. Research on human motor memory reconsolidation suggests that stimulating the hippocampus with rTMS affects not only hippocampal involvement in reconsolidation but also subsequent cortical processing of consolidated episodic memories [**?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**, **?**], enhancing functional connectivity between the PFC and hippocampus [**?**, **?**]. However, no studies have yet reported the application of TMS and tDCS in investigating neural circuits underlying human maladaptive memory reconsolidation. Nevertheless, non-invasive brain stimulation offers a new perspective

for system-level investigation of neural circuit mechanisms and clinical interventions for human maladaptive memory reconsolidation, and its research progress is highly anticipated.

5. Problems and Prospects

The theory of memory reconsolidation has transformed our traditional understanding of long-term memory processing, providing a window of opportunity for modifying established maladaptive memories. Numerous laboratory studies have demonstrated how behavioral or pharmacological methods can intervene in maladaptive memory reconsolidation to weaken or erase established memories. However, the extent to which these laboratory results can serve as feasible and stable interventions for clinical application remains controversial [**?**, **?**].

5.1 "Boundary Conditions" in Reconsolidation Research

"Boundary conditions" in reconsolidation research include memory activation duration, memory age and strength, and cue specificity during memory retrieval [**?**, **?**]. These conditions may be key factors influencing interventions based on reconsolidation principles and represent critical challenges for translating experimental research to clinical application.

Animal studies indicate that during memory activation, if CS presentation is shorter than the CS-US association learning time during acquisition, the established memory cannot be activated to induce reconsolidation. Only when memory activation duration exceeds the learning time can the established memory be effectively activated, though excessively long activation may cause memory extinction rather than reconsolidation [**?**, **?**]. However, effective memory activation times vary considerably across different memory types. In human and animal fear memory research, presenting fear-related cues (approximately 8 seconds to 3 minutes) can activate fear memories [**?**, **?**, **?**]. In contrast, animal studies of inhibitory avoidance indicate that presenting a single cue stimulus (approximately 200 seconds) during memory activation induces memory extinction rather than reconsolidation [**?**, **?**, **?**, **?**, **?**]. Similarly, in food reward conditioning memory models, multiple cue presentations (approximately 10 to 18 times) are required to activate established memories [**?**, **?**], whereas the same number of cue presentations induces memory extinction in human fear conditioning [**?**, **?**]. Therefore, future research should distinguish different types of maladaptive memory and investigate their optimal activation durations or cue presentation numbers.

Memory age and strength also represent key factors determining successful clinical intervention. Newly formed, weak memories are more easily activated and erased or weakened through reconsolidation than exceptionally robust, old memories [**?**, **?**, **?**, **?**, **?**, **?**]. In clinical populations with PTSD, anxiety disorders, and drug addiction, maladaptive memories persist for long periods and are exceptionally robust, posing challenges for clinical intervention. Current research

on intervening in human maladaptive memory remains controversial regarding whether robust, long-standing maladaptive memories can be effectively activated to induce reconsolidation [?, ?, ?]. Animal experiments suggest that extending memory activation duration or increasing the interval between memory formation and activation may facilitate reactivation of strongly retained emotional memories [?, ?, ?]. However, simply extending activation duration may cause memory extinction rather than reconsolidation, and the complexity and intensity of negative emotional memories formed in animals are difficult to compare with human maladaptive memories. Therefore, whether robust, long-standing human maladaptive memories can be activated and how to activate them require further experimental support.

Furthermore, negative emotional memories studied in laboratories typically use simple fear conditioning models with single stimuli and simple association structures, which poorly simulate how humans form fear memories in complex environments. Current research on human maladaptive memory reconsolidation has attempted to use virtual reality technology to present multi-dimensional compound stimuli [?, ?, ?, ?, ?]. However, whether the conditioned stimuli or contextual environments presented during memory reactivation match those during memory acquisition may also affect effective memory activation. This issue remains highly controversial in both animal and human reconsolidation research [?, ?, ?, ?, ?, ?, ?]. In clinical treatment, exposure cues or environments often differ completely from those associated with original maladaptive memory formation. Therefore, the issue of cue specificity during memory activation requires further investigation.

5.2 Complexity of Clinical Intervention

Clinical intervention itself involves considerable complexity. First, individual psychiatric characteristics such as anxiety levels or stress reactivity vary substantially among patients with psychiatric disorders. For example, patients with high avoidance or high anxiety levels have greater difficulty weakening or erasing maladaptive memories using reconsolidation principles [?, ?, ?, ?, ?, ?]. Second, no objective core indicators currently exist to assess whether maladaptive memories have been weakened or erased. For fear memory, most studies show reduced fear responses, such as diminished startle reflex, but findings remain inconsistent regarding whether this erases the CS-US associative memory or weakens US expectancy responses after CS presentation [?, ?, ?, ?].

To effectively intervene in human maladaptive memory, future research should address several key issues. First, reconsolidation research remains primarily limited to animal models, with relatively few studies on human maladaptive memory reconsolidation. Future studies should consider the complex factors involved in human maladaptive memory formation: combine virtual reality technology to simulate clinical environments as closely as possible; distinguish different types of maladaptive memory to investigate optimal activation durations or cue presentation numbers; and analyze the types, structures, and specificity of cues

that effectively activate different maladaptive memories.

Second, core measurement indicators for effectively assessing memory elimination and predicting its recurrence remain undefined, making it impossible to accurately evaluate whether human maladaptive memories have been erased or the degree of weakening. Integrating individual subjective reports, behavioral indicators (e.g., startle reflex, memory retention levels, avoidance behavior), physiological characteristics (e.g., skin conductance, heart rate), and neuroimaging features (e.g., brain region activation levels, neural circuit changes) to analyze specific characteristics of maladaptive memory reconsolidation processing and subsequent memory testing would not only advance understanding of the neural regulatory mechanisms underlying human maladaptive memory reconsolidation but also potentially identify key objective indicators for assessing whether maladaptive memories have been weakened or erased.

Finally, for clinical treatment of human maladaptive memory, researchers should, on one hand, comprehensively apply different non-invasive behavioral intervention techniques, such as extinction training within the reconsolidation window or retrieval-relearning behavioral interventions, while developing stable extinction therapies based on reconsolidation boundary conditions. On the other hand, non-invasive brain stimulation (e.g., TMS, tDCS, and ECT) should be combined with brain imaging techniques to extract specific neural signals during maladaptive memory reconsolidation, further elucidating neural activity characteristics within activated brain regions and functional connectivity between regions, and applying specific frequency stimulation to targeted brain regions or circuits to intervene in maladaptive memory reconsolidation processing. In summary, clinical intervention for human maladaptive memory should fully consider individual patient differences and develop personalized, targeted treatment plans that integrate multiple factors.

References

胡静初, 张蔚欣, 陈小婷, 王文清, 王子洁, 庄楚群, …郑希付. (2019). 远期恐惧记忆再巩固更新机制的线索选择性特点. 心理学报, 51(3), 316-323.

曹杨婧文, 李俊娇, 陈伟, 杨勇, 胡琰健, 郑希付. (2019). 条件性恐惧记忆消退的提取干预范式及其作用的神经机制. 心理科学进展, 27(2), 268-277.

Akagi, K., Yamada, M., Saitoh, A., Oka, J. I., & Yamada, M. (2018). Post-reexposure administration of riluzole attenuates the reconsolidation of conditioned fear memory in rats. *Neuropharmacology, 131*, 1–10.

Alberini, C. M., & Ledoux, J. E. (2013). Memory reconsolidation. *Current Biology, 23*(17), 746–750.

Alfei, J. M., Monti, R. I. F., Molina, V. A., Bueno, A. M., & Urcelay, G. P. (2015). Prediction error and trace dominance determine the fate of fear memories after posttraining manipulations. *Learning & Memory, 22*(8), 1–10.

Agren, T., Engman, J., Frick, A., Bjorkstrand, J., Larsson, E. M., Furmark, T.,

& Fredrikson, M. (2012). Disruption of reconsolidation erases a fear memory trace in the human amygdala. *Science, 337*(6101), 1550–1552.

Beckers, T., & Kindt, M. (2017). Memory reconsolidation interference as an emerging treatment for emotional disorders: Strengths, limitations, challenges, and opportunities. *Annual Review of Psychology, 13*, 99–121.

Bjorkstrand, J., Agren, T., Ahs, F., Frick, A., Larsson, E. M., Hjorth, O., ···Fredrikson, M. (2016). Disrupting reconsolidation attenuates long-term fear memory in the human amygdala and facilitates approach behavior. *Current Biology, 26*(19), 2690–2695.

Bjorkstrand, J., Agren, T., Frick, A., Engman, J., Larsson, E. M., Furmark, T., & Fredrikson, M. (2015). Disruption of memory reconsolidation erases a fear memory trace in the human amygdala: An 18-month follow-up. *Plos One, 10*(7), e0129393.

Blumberger, D. M., Maller, J. J., Thomson, L., Mulsant, B. H., Rajji, T. K., Maher, M., ···Daskalakis, Z. J. (2016). Unilateral and bilateral MRI-targeted repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled study. *Journal of Psychiatry Neuroscience, 41*(4), E58–66.

Boccia, M. M., Blake, M. G., Acosta, G. B., & Baratti, C. M. (2006). Post-retrieval effects of icv infusions of hemicholinium in mice are dependent on the age of the original memory. *Learning & Memory, 13*(3), 376–383.

Brunet, A., Orr, S. P., Tremblay, J., Robertson, K., Nader, K., & Pitman, R. K. (2008). Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *Journal of Psychiatric Research, 42*(6), 503–506.

Censor, N., Dayan, E., & Cohen, L. G. (2014). Cortico-subcortical neuronal circuitry associated with reconsolidation of human procedural memories. *Cortex, 58*, 281–288.

Censor, N., Horovitz, S. G., & Cohen, L. G. (2014). Interference with existing memories alters offline intrinsic functional brain connectivity. *Neuron, 81*(1), 69–76.

Chan, J. C., & LaPaglia, J. A. (2013). Impairing existing declarative memory in humans by disrupting reconsolidation. *Proceedings of the National Academy of Sciences of the United States of America, 110*(23), 9309–9313.

Chan, W. E. M., Leung, H. T., Westbrook, R. F., & McNally, G. P. (2010). Effects of recent exposure to a conditioned stimulus on extinction of Pavlovian fear conditioning. *Learning & Memory, 17*(10), 512–521.

Coles, M. E., & Heimberg, R. G. (2002). Memory biases in the anxiety disorders: Current status. *Clinical Psychology Review, 22*(4), 587–627.

Corinna, B., Paola, B., Giorgio, C., & Marco, D. (2018). Transcranial magnetic stimulation for the treatment of cocaine addiction: Evidence to date. *Substance Abuse and Rehabilitation, 9*, 11–21.

Dayan, E., Censor, N., Buch, E. R., Sandrini, M., & Cohen, L. G. (2013). Noninvasive brain stimulation: From physiology to network dynamics and back. *Nature Neuroscience, 16*(7), 838–844.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3*(1), 11–21.

Diaz-Mataix, L., Ruiz Martinez, R. C., Schafe, G. E., LeDoux, J.E., & Doyere, V. (2013). Detection of a temporal error triggers reconsolidation of amygdala-dependent memories. *Current Biology, 23*(6), 467–472.

Dinur-Klein, L., Dannon, P., Hadar, A., Rosenberg, O., Roth, Y., Kotler, M., & Zangen, A. (2014). Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: A prospective, randomized controlled trial. *Biological Psychiatry, 76*(9), 742–749.

Downar, J., Blumberger, D. M., & Daskalakis, Z. J. (2016). Repetitive transcranial magnetic stimulation: an emerging treatment for medication-resistant depression. *Canadian Medical Association Journal, 188*(16), 1135–1142.

Drexler, S. M., Merz, C. J., Hamacher-Dang, T. C., Tegenthoff, M., & Wolf, O. T. (2015). Effects of cortisol on reconsolidation of reactivated fear memories. *Neuropsychopharmacology, 40*(13), 3036–3043.

Elsey, J. W. B., & Kindt, M. (2017). Tackling maladaptive memories through reconsolidation: From neural to clinical science. *Neurobiology of Learning and Memory, 142*(Pt A), 108–117.

Feng, P., Zheng, Y., & Feng, T. (2015). Spontaneous brain activity following fear reminder of fear conditioning by using resting-state functional MRI. *Scientific Reports, 5*, 16701.

Flavell, C. R., & Lee, J. L. C. (2013). Reconsolidation and extinction of an appetitive Pavlovian memory. *Neurobiology of Learning and Memory, 104*, 25–31.

Gazendam, F. J., Kamphuis, J. H., & Kindt, M. (2013). Deficient safety learning characterizes high trait anxious individuals. *Biological Psychology, 92*(2), 342–352.

Gazendam, F. J., Kamphuis, J. H., Eigenhuis, A., Huizenga, H. M., Soeter, M., Bos, M. G., ···Kindt, M. (2015). Personality predicts individual variation in fear learning: a multilevel growth modeling approach. *Clinical Psychological Science, 3*, 175–188.

Golkar, A., Bellander, M., Olsson, A., & Ohman, A. (2012). Are fear memories erasable?-reconsolidation of learned fear with fear-relevant and fear-irrelevant stimuli. *Frontiers in Behaviour Neuroscience, 6*, 80.

Herrold, A. A., Kletzel, S. L., Harton, B. C., Chambers, R. A., Jordan, N., & Pape, T. L. (2014). Transcranial magnetic stimulation: potential treatment for co-occurring alcohol, traumatic brain injury and posttraumatic stress disorders. *Neural Regeneration Research, 9*(19), 1712–1730.

Hone-Blanchet, A., Wensing, T., & Fecteau, S. (2014). The use of virtual reality in craving assessment and cue-exposure therapy in substance use disorders. *Frontiers in Human Neuroscience, 8*, 844.

Hupbach, A., Hardt, O., Gomez, R., & Nadel, L. (2008). The dynamics of memory: context-dependent updating. *Learning & Memory, 15*(8), 574–579.

Inda, M. C., Muravieva, E. V., & Alberini, C. M. (2011). Memory retrieval and the passage of time: From reconsolidation and strengthening to extinction. *The Journal of Neuroscience, 31*(5), 1635–1643.

Isserles, M., Shalev, A. Y., Roth, Y., Peri, T., Kutz, I., Zlotnick, E., & Zangen, A. (2013). Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder: a pilot study. *Brain Stimulation, 6*(3), 377–383.

Kindt, M., & Soeter, M. (2013). Reconsolidation in a human fear conditioning study: a test of extinction as updating mechanism. *Biological Psychology, 92*(1), 43–50.

Kindt, M., & Soeter, M. (2018). Pharmacologically induced amnesia for learned fear is time and sleep dependent. *Nature Communication, 9*(1), 1316.

Kindt, M., Soeter, M., & Vervliet, B. (2009). Beyond extinction: erasing human fear responses and preventing the return of fear. *Nature Neuroscience, 12*(3), 256–258.

Kroes, M. C., Tendolkar, I., Van Wingen, G. A., Van Waarde, J. A., Strange, B. A., & Fernandez, G. (2014). An electroconvulsive therapy procedure impairs reconsolidation of episodic memories in humans. *Nature Neuroscience, 17*(2), 204–206.

Kwapis, J. L., Jarome, T. J., Ferrara, N. C., & Helmstetter, F. J. (2017). Updating procedures can reorganize the neural circuit supporting a fear memory. *Neuropsychopharmacology, 42*(8), 1688–1697.

Kwapis, J. L., Jarome, T. J., & Helmstetter, F. J. (2015). The role of the medial prefrontal cortex in trace fear extinction. *Learning & Memory, 22*(1), 39–46.

Lee, J. L. C., Nader, K., & Schiller, D. (2017). An update on memory reconsolidation updating. *Trends Cognitive Sciences, 21*(7), 531–545.

Maples-Keller, J. L., Price, M., Jovanovic, T., Norrholm, S. D., Odenat, L., Post, L., ···Rothbaum, B. O. (2017). Targeting memory reconsolidation to prevent the return of fear in patients with fear of flying. *Depress Anxiety, 34*(7), 610–620.

McGaugh, J. L. (2000). Memory—a century of consolidation. *Science, 287*(5451), 248-251.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience, 27*, 1-28.

McGhee, L. L., Maani, C. V., Garza, T. H., Desocio, P. A., Gaylord, K. M., & Black, I. H. (2009). The effect of propranolol on posttraumatic stress disorder in burned service members. *Journal of Burn Care & Research, 30*(1), 92-97.

Merlo, E., Milton, A. L., & Everitt B.J. (2018). A novel retrieval-dependent memory process revealed by the arrest of ERK1/2 activation in the basolateral amygdala. *Journal of Neuroscience, 38*(13), 3199-3207.

Michael, C. S., & Diana, M. (2016). Brain stimulation in addiction. *Neuropsychopharmacology, 41*(12), 2798-2810.

Miniussi, C., Harris, J. A., & Ruzzoli, M. (2013). Modelling non-invasive brain stimulation in cognitive neuroscience. *Neuroscience & Biobehavioral Reviews, 37*(8), 1702-1712.

Mungee, A., Kazzer, P., Feeser, M., Nitsche, M. A., Schiller, D., & Bajbouj, M. (2014). Transcranial direct current stimulation of the prefrontal cortex: a means to modulate fear memories. *Neuroreport, 25*(7), 480-484.

Nader, K. (2015). Reconsolidation and the dynamic nature of memory. *Cold Spring Harbor Perspectives in Biology, 7*(10), a021782.

Nader, K., Schafe, G. E., Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406*(6797), 722-726.

Oyarzun, J. P., Lopez-Barroso, D., Fuentemilla, L., Cucurell, D., Pedraza, C., Rodriguez-Fornells, A., & de Diego-Balaguer, R. (2012). Updating fearful memories with extinction training during reconsolidation: A human study using auditory aversive stimuli. *PLoS One, 7*(6), e38849.

Piñeyro, M. E., Monti, R. I. F., Alfei, J. M., Bueno, A. M., & Urcelay, G. P. (2014). Memory destabilization is critical for the success of the reactivation-extinction procedure. *Learning & Memory, 21*(1), 46-54.

Pitman, R. K. (1989). Post-traumatic stress disorder, hormones, and memory. *Biological Psychiatry, 26*(3), 221-223.

Pitman, R. K., Sanders, K. M., Zusman, R. M., Healy, A. R., Cheema, F., Lasko, N. B., ···Orr, S. P. (2002). Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biological Psychiatry, 51*(2), 189-192.

Power, A. E., Berlau, D. J., McGaugh, J. L., & Steward, O. (2006). Anisomycin infused into the hippocampus fails to block 'reconsolidation' but impairs extinction: The role of re-exposure duration. *Learning & Memory, 13*(1), 27-34.

Preston, A. R., & Eichenbaum, H. (2013). Interplay of hippocampus and prefrontal cortex in memory. *Current Biology, 23*(17), 764–773.

Reznikov, R., & Hamani, C. (2017). Posttraumatic Stress Disorder: Perspectives for the Use of Deep Brain Stimulation. *Neuromodulation, 20*(1), 7–14.

Robinson, M. J. F., & Franklin, K. B. J. (2010). Reconsolidation of a morphine place preference: Impact of the strength and age of memory on disruption by propranolol and midazolam. *Behavioural Brain Research, 213*(2), 201–207.

Rosenbaum, S., Vancampfort, D., Steel, Z., Newby, J., Ward, P. B., & Stubbs, B. (2015). Physical activity in the treatment of Post-traumatic stress disorder: A systematic review and meta-analysis. *Psychiatry Research, 230*(2), 130–136.

Sandrini, M., Censor, N., Mishoe, J., & Cohen, L. G. (2013). Causal role of prefrontal cortex in strengthening of episodic memories through reconsolidation. *Current Biology, 23*(21), 2181–2184.

Schiller, D., Kanen, J. W., LeDoux, J. E., Monfils, M. H., & Phelps, E. A. (2013). Extinction during reconsolidation of threat memory diminishes prefrontal cortex involvement. *Proceedings of the National Academy of Sciences of the United States of America, 110*(50), 20040–20045.

Schiller, D., Monfils, M. H., Raio, C. M., Johnson, D. C., Ledoux, J. E., & Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature, 463*(7277), 49–53.

Schwabe, L., Nader, K., Wolf, O. T., Beaudry, T., & Pruessner, J. C. (2012). Neural signature of reconsolidation impairments by propranolol in humans. *Biological Psychiatry, 71*(4), 380–386.

Schwabe, L., Nader, K., & Pruessner, J. C. (2013). -Adrenergic blockade during reactivation reduces the subjective feeling of remembering associated with emotional episodic memories. *Biological Psychology, 92*(2), 227–232.

Sevenster, D., Beckers, T., & Kindt, M. (2012). Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. *Neurobiology of Learning and Memory, 97*(3), 338–345.

Sevenster, D., Beckers, T., & Kindt, M. (2013). Prediction error governs pharmacologically induced amnesia for learned fear. *Science, 339*(6121), 830–833.

Sevenster, D., Beckers, T., & Kindt, M. (2014). Prediction error demarcates the transition from retrieval, to reconsolidation, to new learning. *Learning & Memory, 21*(11), 580–584.

Shafi, M. M., Westover, M. B., Fox, M. D., & Pascual-Leone, A. (2012). Exploration and modulation of brain network interactions with noninvasive brain stimulation in combination with neuroimaging. *European Journal of Neuroscience, 35*(6), 805–825.

Shehata, M., Abdou, K., Choko, K., Matsuo, M., Nishizono, H., & Inokuchi, K. (2018). Autophagy enhances memory erasure through synaptic destabilization. *Journal of Neuroscience, 38*(15), 3809–3822.

Shiban, Y., Brutting, J., Pauli, P., & Muhlberger, A. (2015). Fear reactivation prior to exposure therapy: Does it facilitate the effects of VR exposure in a randomized clinical sample? *Journal of Behavior Therapy and Experimental Psychiatry, 46*, 133–140.

Soeter, M., & Kindt, M. (2010). Dissociating response systems: erasing fear from memory. *Neurobiology of Learning and Memory, 94*(1), 30–41.

Soeter, M., & Kindt, M. (2011). Disrupting reconsolidation: pharmacological and behavioral manipulations. *Learning & Memory, 18*(6), 357–366.

Soeter, M., & Kindt, M. (2012a). Erasing fear for an imagined threat event. *Psychoneuroendocrinology, 37*(11), 1792–1798.

Soeter, M., & Kindt, M. (2012b). Stimulation of the noradrenergic system during memory formation impairs extinction learning but not the disruption of reconsolidation. *Neuropsychopharmacology, 37*(5), 1204–1215.

Soeter, M., & Kindt, M. (2013). High trait anxiety: A challenge for disrupting fear reconsolidation. *Plos One, 8*(11), e75239.

Soeter, M., & Kindt, M. (2015). An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. *Biological Psychiatry, 78*(12), 880–886.

Suzuki, A., Josselyn, S. A., Frankland, P. W., Masushige, S., Silva, A. C., & Kida, S. (2004). Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *The Journal of Neuroscience, 24*(20), 4787–4795.

Taylor, J. R., & Torregrossa, M. M. (2015). Pharmacological disruption of maladaptive memory. *Handbook of Experimental Pharmacology, 228*, 381–415.

Thome, J., Koppe, G., Hauschild, S., Liebke, L., Schmahl, C., Lis, S., & Bohus, M. (2016). Modification of fear memory by pharmacological and behavioural interventions during reconsolidation. *Plos One, 11*(8), e0161044.

Treanor, M., Brown, L. A., Rissman, J., & Craske, M. G. (2017). Can memories of traumatic experiences or addiction be erased or modified? A critical review of research on the disruption of memory reconsolidation and its applications. *Perspectives on Psychological Science, 12*(2), 290–305.

Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A., & Marmar, C. R. (2003). Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biological Psychiatry, 54*(9), 947–949.

Warren, V. T., Anderson, K. M., Kwon, C., Bosshardt, L., Jovanovic, T., Bradley, B., & Norrholm, S. D. (2014). Human fear extinction and return

of fear using reconsolidation update mechanisms: the contribution of on-line expectancy ratings. *Neurobiology of Learning and Memory, 113*, 165–173.

Wood, N. M., Rosasco, M. L., Suris, A. M., Spring, J. D., Marin, M. F., Lasko, N. B., & Pitman, R. K. (2015). Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: Three negative psychophysiological studies. *Psychiatry Research, 225*(1-2), 30–39.

Xue, Y. X., Luo, Y. X., Wu, P., Shi, H. S., Xue, L. F., Chen, C., & Lu, L. (2012). A memory retrieval-extinction procedure to prevent drug craving and relapse. *Science, 336*(6078), 241–245.

Zlomuzica, A., Dere, D., Machulska, A., Adolph, D., Dere, E., & Margraf, J. (2014). Episodic memories in anxiety disorders: clinical implications. *Frontiers in Behaviour Neuroscience, 8*, 131.

Zubedat, S., & Akirav, I. (2017). The involvement of cannabinoids and mTOR in the reconsolidation of an emotional memory in the hippocampal-amygdala-insular circuit. *European Neuropsychopharmacology, 27*(4), 336–349.

Note: Figure translations are in progress. See original paper for figures.