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Memory Creation and Modification: Enhancing the Treatment of Psychological Disorders

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Abstract

Modification of the ongoing influence of maladaptive cognitive, emotional, and behavioral patterns is a fundamental feature of many psychological treatments. Accordingly, a clear understanding of the nature of memory adaptation and accommodation to therapeutic learning becomes an important issue for (1) understanding the impact of clinical interventions, and (2) considering innovations in treatment strategies. In this article, we consider advances in the conceptualization of memory processes and memory modification research relative to clinical treatment. We review basic research on the formation of memories, the way in which new learning is integrated within memory structures, and strategies to influence the nature and degree to which new learning is integrated. We then discuss cognitive/behavioral and pharmacological strategies for influencing memory formation in relation to disorder prevention or treatment. Our goal is to foster awareness of current strategies for enhancing therapeutic learning and to encourage research on potential new avenues for memory enhancement in service of the treatment of mental health disorders.

Keywords

memory; consolidation; reconsolidation; psychotherapy; exposure therapy

If one goal of psychotherapy is to modify the degree to which individuals are emotionally or behaviorally shackled by their own learning histories, then a clear understanding of the nature of memory adaptation and accommodation to new information becomes an important issue for the enhancement of clinical interventions. The purpose of this paper is to provide a clinically-focused review on (1) the formation of memories and the way in which new learning is integrated within existing memory structures, and (2) cognitive/behavioral and pharmacological strategies for influencing memory in service of the prevention and treatment of psychological disorders. The ultimate goal of this paper is to support the translation of these strategies to the clinic to aid in the treatment of psychological disorders.

Memory formation and the way in which new learning is integrated within existing memory structures has rich clinical relevance because, regardless of theoretical orientation,

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psychotherapy is often concerned with reducing the influence of an individual's personal history on his/her current functioning. For example, according to object relations theorists (e.g., Hamilton, 1989) the way individuals relate to others and situations in their adult lives is shaped by family experiences during infancy, helping to determine the ways in which individuals predict and mispredict the actions of others. Successful therapy helps individuals not be dominated by these earliest memories and to develop more adaptive responses to current individuals and events in their lives.

The focus on engendering new learning to replace maladaptive patterns is more central to cognitive-behavioral approaches, with focused efforts to help individuals free themselves from the cognitions, core beliefs, and emotional reactions that are shaped by previous experiences. Cognitive interventions help individuals actively learn to identify historical thinking biases, substitute accurate here-and-now interpretations for biased cognitions, and/or change emotional responsivity to cognitions. These efforts may be aided by core-belief work, where thematic learned responses are tied to early critical incidents and are changed through active disputation (Beck, 2011). Moreover, perhaps the clearest examples of work to unshackle individuals from their own learning histories occur with cognitive-behavioral treatments for anxiety and traumatic stress disorders. For these disorders, state-of-the-art treatment involves information, cognitive-restructuring, and exposure interventions to help patients relearn a sense of safety in relation to feared situations and events (Olatunji, Cisler, & Deacon, 2010).

To conceptualize the latter process, it is helpful to consider the original fear learning as a network of associations (a complex set of memories) which exists across multiple sensory modalities and involves language-based abstractions of the fears (Lang, Davis, & Öhman, 2000). Considering fear learning as a network of associations is an apt conceptualization regardless of the source of the original fear memories, including direct conditioning experience, misinformation, and modeling (Olsson & Phelps, 2007). As a result of these learning histories, acquired fears can be conceptualized as a set of memories that, in their more extreme forms, engender the outcome expectancies, emotions, and behaviors that define anxiety disorders (e.g., Bouton, Mineka, & Barlow, 2001). It is also important to note that this set of memories includes acquired conditioned responses, as well as episodic memories of experiences during which conditioned responses were formed. Both potentially contribute to psychopathology (Dere, Pause, & Pietrowsky, 2010).

Staying with the example of fear-relevant memories, there are a number of strategies to consider for influencing the strength of these memories. One method is to prevent strong fear memories from developing in the first place by intervening immediately after fear learning to attenuate consolidation. It is not always feasible, however, to intervene immediately. Once fear memories are established, recovery from their influence involves active new learning of safety. In many cases, these new memories of relative safety in the presence of fear cues (e.g., as occurring after successful treatment) exist in competition with the original fear memories (Bouton, 2002). When therapeutic learning is effective, the memories of relative safety come to dominate. Yet these memories of safety can be richly dependent on context, and relapse can be understood as the re-emergence of the dominance of the original fear memories. However, there is also evidence that, under the right

conditions, specialized interventions can be used to at least partially replace the original fear memories, leading to conditions where relapse is less likely (for review, see Kredlow, Unger, & Otto, 2016). In addition, there is an increasing number of augmentation strategies to help set in stronger therapeutic memories, jump-starting the process of making safety memories more dominant. These strategies could potentially decrease the amount of therapy needed to achieve meaningful clinical outcomes.

These novel strategies for reducing fears underscore the potential promise of a new subfield of clinical augmentation research that is dependent on a fuller understanding of the role of memory processes in therapeutic outcome. In the following sections we provide a conceptual overview of the core processes involved in memory creation, integration, and modification and a comprehensive review of research findings on augmentation strategies for memory modification.

Memory Creation, Integration, and Modification

Memories are created through a process called *consolidation* (Dudai, 2004) during which newly learned information transforms from a labile to more permanent state. During the consolidation process, memories are susceptible to interference and consolidation is thus inferred from a time window of susceptibility to amnesic agents. Within a few hours of initial learning, if an amnesic agent is administered, consolidation is blocked, leading to retrograde amnesia (Schafe & LeDoux, 2000). After more time has passed, however, amnesic agents no longer have an effect on the memory.

What is actually happening in the brain during the process of memory creation? Researchers have examined consolidation from a large scale (i.e., brain system level) and a small scale (i.e., synaptic level). Synaptic level consolidation is thought to occur within hours of learning, whereas brain system level consolidation can take weeks, months, or even years (Dudai, 2004). At the brain system level, predominant theories posit that consolidation involves the hippocampus and the neocortex (McKenzie & Eichenbaum, 2011). Immediately after initial learning, the memory trace depends on modifications of network connectivity within the hippocampus that link cortical representations of the elements of an experience. This process may involve a combination of existing neurons as well as new neurons produced in the hippocampus (e.g., Toni et al., 2007). Over time, semantic knowledge derived from a memory may be fully stored in the neocortex by integration with related memories in cortical networks, whereas the episodic content will always somewhat rely on connections between the hippocampus and neocortex (Nadel, Samsonovich, Ryan, & Moscovitch, 2000). Although many areas of the neocortex are involved, connections between the prefrontal cortex (PFC) and the hippocampus support memory consolidation (Preston & Eichenbuam, 2013). For fear memories, research has demonstrated involvement of the hippocampus, amygdala, and PFC in acquisition and extinction (for review, see Maren, 2001).

Given that the brain is not a blank slate, a central component of the process of consolidation is integrating new information into an existing memory structure (McKenzie & Eichenbaum, 2011). The existing memory structure can be envisioned as a network of interconnected

neurons within the hippocampus and neocortex with overlapping neurons for related memories. Research suggests that when a new memory is integrated into this network it occurs through one of two means: *assimilation* or *accommodation* (for review, see Landmann et al., 2014). Assimilation occurs when a new memory is integrated into the network in a manner that leaves old memories intact. This process of integration is not random but instead appears to follow distinct patterns (Silva, Zhou, Rogerson, Shobe, & Balaji, 2009). At a cortical level, Wang and Morris (2010) demonstrated that consolidation can occur more rapidly if a schema already exists for the knowledge, leading to the concept of rapid schema consolidation. Rapid schema consolidation explains why information that fits within a schema that we already have learned can be learned faster than information that contradicts preexisting schemas (Tse et al., 2007).

The second method through which new information can be integrated into existing memory structures is called accommodation. In contrast to assimilation, during accommodation, a preexisting memory formation is disrupted and transformed by the new information. The process of accommodation requires *reconsolidation* of the preexisting memory. As with consolidation, during reconsolidation, memories are malleable and susceptible to interference or updating. The reconsolidation window of susceptibility is also time-limited (thought to be within 10 mins – 6 hrs). Reconsolidation is similarly demonstrated in effect by its absence. When a previously consolidated memory is reactivated, usually with a reminder of that memory, and an amnesic agent or other intervention aimed at interfering with the memory is administered soon after, amnesia for or a weakening of that memory typically occurs. If more time has passed, however, the agent or intervention has no impact on the memory (Nader, Schafe, & LeDoux, 2000). Thus, reactivation of an old memory presents a small window of time during which that memory can be reconsolidated and memory accommodation can occur.

Augmentation Strategies for Memory Modification

In the following sections, we consider novel cognitive/behavioral and pharmacological interventions that have been applied to modify memory consolidation or reconsolidation in service of clinical outcomes. These interventions include: (1) preventive efforts directed at inhibiting maladaptive memory formation, (2) strategies to interfere with the reconsolidation of maladaptive learning, and (3) strategies to enhance the consolidation of new therapeutic learning.

1. Modifying Memory Formation to Prevent Disorder Onset

One approach is to target memories immediately upon formation and to interfere with the consolidation and/or assimilation process. Researchers have investigated pharmacological and behavioral strategies to do so and this research has been translated from the animal to human laboratory and, further, to the clinic in applications with patients. To date, strategies targeting memory consolidation have focused on fear memories given the clear relevance for targeting trauma memories that underlie traumatic stress disorders. However, some research indicates that these strategies may also impact declarative memories.

Pharmacological strategies—Researchers have been exploring methods to pharmacologically interfere with fear memory consolidation for over two decades. Early animal studies demonstrated that administration of a protein synthesis inhibitor immediately after (compared to 6 hrs after) fear conditioning resulted in interference with the consolidation of a fear memory (Schafe & LeDoux, 2000). Similarly, researchers found that administration of the B-adrenergic antagonist propranolol during or immediately after fear conditioning could block memory consolidation in animals (Cahill, Pham, & Setlow, 2000). As propranolol is safe for use in humans, this work was subsequently translated to the clinic.

Propranolol: Researchers first demonstrated interference with the consolidation of memories in humans using emotionally arousing stories followed by the administration of propranolol immediately after story learning (Cahill, Prins, Weber, & McGaugh, 1994). A meta-analysis of 10 studies conducted with healthy participants demonstrated a medium significant effect of propranolol for interfering with the consolidation of negative memories (Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013). Subsequently, it was hypothesized that administering propranolol immediately after a traumatic event could prevent the development of posttraumatic stress disorder (PTSD; Pitman et al., 2002). A series of studies were then conducted with emergency-room patients soon after trauma exposure. Although initial pilot study results were promising (Pitman et al., 2002), a meta-analysis of four subsequent trials did not find a difference in the rates of PTSD symptom development (Argolo, Cavalcanti-Ribeiro, Netto, & Quarantini, 2015). These results ultimately did not support the use of propranolol to prevent the consolidation of traumatic memories. One issue, however, was the length of time that propranolol was used – in some cases, continuing up to 19 days (Argolo et al., 2015). As a result, propranolol may have not only inhibited the formation of fear memories, but also inhibited the reacquisition of safety in relation to fear cues (for discussion, see Otto, McHugh, & Kantak, 2010).

Although propranolol research has mainly focused on interfering with the consolidation of fear memories, there is some indication that it may also influence emotional declarative memories. For example, many of the studies in the meta-analysis examining propranolol (Lonergan et al., 2013) presented participants with emotionally upsetting stories, words, or images and later tested for declarative memory recall. Nonetheless, studies targeting conditioned fear memories, have emphasized that propranolol targets the physiological fear response but not declarative aspects of the conditioned fear. Specifically, participants were still aware of the conditioned stimulus (CS)-unconditioned stimulus (UCS) contingency after the procedure (for review, see Schwabe, Nader, & Pruessner, 2014). The use of propranolol to interfere with trauma memory consolidation is a topic of debate given ethical concerns about interfering with declarative aspects of trauma memories (Henry, Fishman, & Youngner, 2007).

Cortisol: Despite the disappointing results via propranolol, more promising results have been found with cortisol. Cortisol is a glucocorticoid that is naturally released by the adrenal cortex in response to stress. The effect of cortisol on memory consolidation is thought to follow an inverted U-shaped curve in that moderate doses enhance memory consolidation whereas lower and higher doses may impair consolidation (de Quervain, Schwabe, &

Roozendaal, 2017). Animal research on cortisol/hydrocortisone has been translated to work with patients, with a recent meta-analysis reporting a large significant effect of post-trauma administration of high doses of cortisol on preventing the development of PTSD symptoms (Sijbrandi, Kleiboer, Bisson, Barbui, & Cuijpers, 2015). Cortisol/hydrocortisone also appears to interfere with declarative memory consolidation to some degree (de Quervain et al., 2017).

Other agents: Additional pharmacological means to interfere with consolidation still remain to be explored. For example, given promising findings in animals (e.g., Cohen et al., 2010), a trial is underway examining the administration of oxytocin to emergency-room patients with recent trauma exposure. The goal of oxytocin administration is to interfere with the danger signal from the trauma by providing hormonal cues for interpersonal bonding and trust (Frijling et al., 2014). Other agents being explored include rapamycin (Mac Callum, Hebert, Adamec, & Blundell, 2014), ketamine (Juven-Wetzler et al., 2014), garcinia indica (Fuchs & McLaughlin, 2016), morphine, and albuterol (Sijbrandij et al., 2015).

Cognitive and behavioral strategies

Extinction during consolidation: In light of the limited success of pharmacological strategies, researchers have begun to examine behavioral strategies to interfere with fear memory consolidation. One strategy involves manipulating the typical timing of extinction. Specifically, Myers, Ressler, and Davis (2006) found that administering extinction trials immediately following acquisition, compared to 24 hours after acquisition, interfered with the consolidation of fear learning and prevented the return of fear in rats. By timing extinction while fear memories are still being assimilated, fear memories and extinction memories may be assimilated together. This hypothesis is supported by animal research showing that contextual memories encoded close in time are linked by overlapping groups of neurons in the hippocampus (Cai et al., 2016). Researchers are currently translating the strategy of administering extinction immediately following acquisition to the clinic by administering exposure therapy in the emergency room shortly after trauma exposure. In an initial pilot study by Rothbaum and colleagues (2012), individuals who received prolonged exposure within 3 days of trauma reported lower PTSD symptoms 4 and 12 weeks post-trauma. Although there may be multiple mechanisms involved, including the modification of system level rather than synaptic level consolidation (Dudai, 2004), this research suggests that conducting exposure therapy soon after trauma may modify the consolidation or assimilation of the trauma memory and help prevent the development of PTSD.

Sleep: Sleep disruption can play an important role in inhibiting memory consolidation, particularly schema formation and integration which seem to rely on slow wave sleep (Landmann et al., 2014). In particular, fear conditioning studies in animals (e.g., Kumar & Jha, 2012) and healthy humans (Menz et al., 2013) indicate that sleep deprivation can disrupt fear memory consolidation. In a recent pre-clinical application, Porcheret, Holmes, Goodwin, Foster, and Wulff (2015) examined the impact of sleep deprivation following exposure to a traumatic film on later intrusive memories in healthy adults. Their results indicated that sleep deprivation led to a reduction of intrusive emotional memories about the

film. These findings have led some to question whether sleep deprivation following trauma exposure may be a means to interfere with trauma memory consolidation and prevent PTSD (Porcheret et al., 2015). However, it is important to note that sleep also plays a role in declarative memory consolidation (Landmann et al., 2014). Thus, sleep deprivation after a traumatic event would likely also impact the consolidation of declarative aspects of the trauma to some degree.

In a study conducted by Hauner, Howard, Zelano, and Gottfried (2013), sleep was harnessed in a different way to interfere with fear memory consolidation. Participants underwent fear conditioning where faces were associated with shocks in a target context (represented by an odor). Conditioning was immediately followed by a nap during which the fear memory was extinguished by continuous presentation of the odor without shocks during slow wave sleep. Exposure to the odor during the nap resulted in reduced fear responses to the faces when participants were tested later during waking hours. Conducting the same procedures while participants were awake had no effect. These findings suggest that sleep, and specifically slow wave sleep, may present a particularly useful time window to attempt to interfere with the consolidation of fear memories by administering immediate extinction.

Brain stimulation and neuromodulation: Given the role of the PFC in supporting memory consolidation, studies have examined brain stimulation and neuromodulation of the PFC as a method to interfere with the consolidation of conditioned fear memories. One study (Asthana et al., 2013) demonstrated that cathodal (i.e., inhibitory) transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique, of the left dorsolateral PFC for 12 minutes immediately after fear conditioning in humans interfered with memory consolidation. Another fear conditioning study in humans (Guhn et al., 2014) used transcranial magnetic stimulation (TMS) of the medial PFC between acquisition and extinction and found reduced CS+/CS- discrimination during extinction. However, based on the timing of the administration of the TMS in Guhn and colleagues' (2013) study, it is unclear whether the TMS interfered with the consolidation of the fear learning or enhanced extinction learning.

Limitations of strategies targeting memory consolidation—One challenge in translating animal studies of interference with the consolidation of fear memories to the clinic has been the difficulty of intervening with patients soon after a trauma occurs. Since laboratory studies administer agents immediately after acquisition, they likely impact synaptic level consolidation. In contrast, clinic studies are not reaching patients until many hours or days after a trauma occurs, at which point synaptic level consolidation is likely complete and strategies impact brain system level consolidation. Additionally, there is some indication that consolidation interference is less likely to be effective after more time has passed (Argolo et al., 2015). Given this limitation, researchers have explored methods to influence fear memories even after time has passed, namely by targeting memory reconsolidation.

2. Interfering with Memory Reconsolidation for Clinical Benefit

Targeting the reconsolidation of memories is another avenue that has been explored in the animal and human laboratory, with translation of some strategies to the clinic. Pharmacological strategies have attempted to completely block the reconsolidation of fear memories, thereby weakening these memories. Behavioral strategies have used the reconsolidation window to update fear memories with new information, allowing for integration of safety memories through accommodation. Some of these strategies have also been applied outside fear memories to emotional episodic memories and appetitive memories, with potential applications for the treatment of affective and other disorders.

Pharmacological strategies—The clinical research agenda of interfering with memory reconsolidation was set into action by Nader and colleagues (2000) who found that during the time period following memory reactivation, a memory is sensitive to disruption. Specifically, using a de novo fear conditioning paradigm, Nader et al. (2000) showed that administration of a protein-synthesis inhibitor in the amygdala of the rat, following presentation of a memory retrieval cue of the conditioned stimulus (i.e., a tone), could block the return of fear. This procedure resulted in amnesia for a fear memory up to 14 days after conditioning. Additional studies demonstrated that this procedure prevents renewal, reinstatement, and spontaneous recovery of fear which are commonly seen even after successful extinction, indicating that this paradigm is not enhancing extinction but interfering with reconsolidation (Duvarci & Nader, 2004). The distinction between reconsolidation interference and enhanced extinction is also supported by research demonstrating distinct temporal and biochemical signatures of reconsolidation versus extinction (Suzuki et al., 2004).

Propranolol: Nader et al.'s (2000) reconsolidation blockade strategy has been replicated and extended to humans, using propranolol during the reconsolidation window. A meta-analysis of post-retrieval propranolol to interfere with the reconsolidation of conditioned fear memories and negative emotional declarative memories (Lonergan et al., 2013) reports an overall significant moderate effect size. Interestingly, there was no difference in effect sizes for studies examining conditioned fear memories and studies examining emotional declarative memories, indicating that propranolol may also have potential applications for negative declarative memories and the treatment of non-fear-based disorders (Schwabe et al., 2014). Studies published since the meta-analysis, have provided a mixed picture on the reliability of this effect for conditioned fear memories. Whereas the effect was replicated in studies that used fear-irrelevant stimuli for conditioning (e.g., Sevenster, Beckers, & Kindt, 2012; Soeter & Kindt, 2012) the effect was not replicated in a study that used fear-relevant stimuli (i.e., spiders; Spring et al., 2015).

In a translation of these findings to a laboratory study with patients, Brunet and associates (2008) examined one-time administration of propranolol versus placebo after retrieval of a traumatic memory in PTSD patients. Significantly smaller physiologic responses in the propranolol group were observed a week later when engaged in mental imagery of their traumatic event. Likewise, Soeter & Kindt (2015) demonstrated propranolol-induced disruption of the reconsolidation of spider-fear memories, with clinical benefits maintained

up to 1 year after treatment. Soeter & Kindt's (2015) finding is noteworthy given the lack of effectiveness for prepared fears in the aforementioned conditioning study (Spring et al., 2015). It is also consistent with uncontrolled reports of propranolol enhancement of clinical outcomes in PTSD (Brunet et al., 2011). Nonetheless, these promising findings are tempered by a study similar to Brunet et al. (2008), conducted by Wood et al. (2015), which found that one-time administration of propranolol versus placebo did not interfere with the reconsolidation of traumatic memories in PTSD patients.

Propranolol research has also been extended outside of anxiety and traumatic stress disorders. Reactivating addiction-related memories under propranolol has been explored as a means to interfere with memories for craving and cue reactivity in substance users. Results of these studies, however, are mixed (for review, see Dunbar & Taylor, 2016).

Mifepristone: Although propranolol has been the primary drug investigated to interfere with fear memory reconsolidation in humans, other drugs have also been explored. A recent pilot study attempted to translate the animal work with glucocorticoid antagonist RU38486 (i.e., mifepristone) to humans by examining the impact of post-retrieval mifepristone versus placebo on the reconsolidation of traumatic memories in PTSD patients (Wood et al., 2015). However, no differences in responding during a script-driven traumatic mental imagery task were found between the groups. As this study only involved one-time administration of mifepristone and was limited in sample size, further research is underway.

Cortisol: Cortisol has also been explored as an agent for inhibiting the retrieval of fear memories and thereby interfering with reconsolidation of these memories. De Quervain and Margraf (2008) found that administering a low-dose of cortisol to PTSD patients for 1 month resulted in reduced symptoms of traumatic memories compared to placebo. Another study which administered cortisol to PTSD patients for 1 week, however, failed to demonstrate benefits (Ludäscher et al., 2015). There is also some indication that cortisol may be beneficial for reducing retrieval of fear memories in social phobia (for review, see de Quervain et al., 2017). In line with studies on cortisol, researchers have also explored inducing stress after fear memory reactivation as a method to interfere with memory reconsolidation (Drexler & Wolf, 2017). In addition, cortisol and stress are being explored to interfere with the reconsolidation of episodic (Schwabe et al., 2014) and appetitive memories (de Quervain et al., 2017).

Other agents: Other agents in the early stages of testing include cannabidiol (Jurkus et al., 2016), ketamine (Duclot, Perez-Taboada, Wright, & Kabbaj, 2016), xenon (Meloni, Gillis, Manoukian, & Kaufman, 2014), sirolimus (Surís, Smith, Powell, & North, 2013), rapamycin (Mac Callum et al., 2014), and garcinia indica (Dunbar & Taylor, 2016). Some of these agents are also being explored as means to interfere with the reconsolidation of appetitive memories (for review, see Torregrossa & Taylor, 2016).

Cognitive and behavioral strategies

Post-retrieval extinction: In 2009, another innovation was introduced for modifying fear memories. Rather than using pharmacologic strategies to interfere with memory

reconsolidation, Monfils, Cowansage, Klann, and LeDoux (2009) examined the role of extinction learning during the reconsolidation window in animals. Specifically, they showed that extinction following a memory retrieval cue (i.e., post-retrieval extinction) was more effective than extinction that was not conducted during the reconsolidation window. This intervention was predicated on the theory that reconsolidation is not only a mechanism for re-solidifying a memory but also a mechanism for "updating" a memory with new information (McKenzie & Eichenbaum, 2011). In this case, the fear memory is updated with information about safety provided through extinction learning. Theoretically, memory accommodation rather than assimilation occurs. Efforts have been made to replicate this finding in animals with mixed results, although a recent meta-analysis of these studies (Kredlow et al., 2016) indicates that variations in experimental methods may explain a portion of the heterogeneity in effects observed.

Subsequently, Schiller and colleagues (2010) tested this protocol in humans. Healthy participants underwent fear acquisition. One day later, participants were randomized to (1) extinction without a memory retrieval cue, (2) extinction 10 minutes after a memory retrieval cue (a single presentation of the CS+ from acquisition), or (3) extinction 6 hours after a memory retrieval cue (i.e., extinction outside the presumed reconsolidation window). Participants who received post-retrieval extinction (condition 2) demonstrated significantly less return of fear when tested 1 day later, with some evidence of maintenance of this effect 1 year later (Schiller et al., 2010). In contrast, fear returned in the groups that received traditional extinction (condition 1) and extinction outside of the reconsolidation window (condition 3), which is the typical pattern largely observed across extinction studies (Bouton, 2002). In a within-participant design follow up study, Schiller and colleagues (2010) also demonstrated that the interference produced by post-retrieval extinction was specific to the retrieved memory, not associated memories.

Since Schiller et al. (2010), multiple studies have replicated this finding with conditioned fear memories. A recent meta-analysis (Kredlow et al., 2016) examining these studies reported an overall significant positive small-moderate effect of post-retrieval extinction over traditional extinction in preventing the return of conditioned fear in humans. Interestingly, the effect size of post-retrieval extinction was similar in magnitude to that of propranolol for interference with the reconsolidation of fear memories. While the overall effect was significant, the fear-relevance of the conditioned stimuli moderated post-retrieval extinction effects. Specifically, post-retrieval extinction was less effective for fear-relevant stimuli, similar to the findings regarding propranolol described above. Nonetheless, overall positive effects encourage the translation of post-retrieval extinction to the clinic.

To our knowledge, only two pilot studies have attempted to apply post-retrieval extinction to a clinical population with anxiety. Shiban, Brütting, Pauli, and Mühlberger (2015) had spider phobic patients undergo virtual reality exposure therapy with or without a 5-second fear reactivation procedure 10 minutes prior to exposure. Participants in the post-retrieval extinction group did not differ from the exposure only group in a spontaneous recovery test or follow up assessments of fear. In contrast, Telch, York, Lancaster, and Monfils (2017) did find compelling evidence of post-retrieval extinction effects in a study of spider and snake phobic participants. In this study, in the post-retrieval extinction group, a 10 second fear

reactivation procedure was followed by a 30-minute break, then initiation of in vivo exposure therapy. Participants in the post-retrieval extinction group, compared to an exposure only group, displayed lower phobic responding at one-month follow up. It is possible that these discrepant results may be due to differences in the reactivation procedure, the amount of exposure administered, or other aspects of the study designs. Further research is needed to understand how to best translate post-retrieval extinction into a therapeutic format and to date, no studies have been published examining post-retrieval extinction in patients with other anxiety or traumatic stress disorders. Nonetheless, there has also been early application of post-retrieval extinction to conditioned disgust memories, with minimal support for this application (Olatunji, Sarawgi, & Viar-Paxton, 2016).

In addition, there is a growing body of literature examining interference with the reconsolidation of appetitive memories with potential implications for the treatment of substance use disorders (Torregrossa & Taylor, 2016). Multiple studies have examined post-retrieval extinction for appetitive memories in animals with overall large significant effects on preventing the return of appetitive responses compared to extinction (Kredlow et al., 2016). Thus far, only one study has attempted to translate these findings to work with humans, showing promising effects in a sample of heroin addicts (Xue et al., 2012).

Episodic memory strategies: Much of the literature to date has focused on interfering with the reconsolidation of fear-based or appetitive drug memories with the goal of improving treatments for anxiety and traumatic stress disorders or substance use disorders. However, behavioral reconsolidation interference strategies also have implications for treatments that do not rely on formal extinction procedures. For example, cognitive restructuring procedures for depression make use of the re-evocation of an upsetting event and then reinterpretation of the meaning of that event using Socratic questioning or other procedures (Beck, 2011). At times, these strategies are applied to specific early memories and associated generalized beliefs that may have outsized influences on dysfunctional interpretations of current events. Restructuring of the meaning of these early memories is a focus of core belief work (Beck, 2011). Core belief work may involve specific recall of early life events that engendered or supported core negative beliefs about the self. It is an open question whether these procedures might be aided by more formal reactivation of the early memories and then targeting restructuring within the resulting reconsolidation window. Procedurally, a clearer focus on two distinct phases for the intervention would be needed: (1) the activation of a known, relevant memory and then (2) a subsequent focus on integrating new information (i.e., more benign interpretations) into the memory. Non-clinical studies have provided initial support for this approach, showing that retrieval followed by an alternative narrative can be used to interfere with the reconsolidation of relatively recent episodic memories (Kredlow & Otto, 2015; Schwabe et al., 2014). These early findings encourage further evaluation of the application of reconsolidation interference procedures for the emotional episodic memories that play an important role in the etiology and maintenance of a range of emotional and affective disorders (Dere et al., 2010).

The focus on modifying upsetting or inappropriately influential memories is also characteristic of imagery rescripting approaches (Morina, Lancee, & Arntz, 2017). Imagery rescripting is an intervention that involves the reactivation of a preexisting unpleasant

memory followed by a retelling of that memory with the use of benign or positive images. Imagery rescripting has been applied to a range of disorders including PTSD, social anxiety disorder, body dysmorphic disorder, bulimia nervosa, major depression, and obsessive compulsive disorders (OCD), with a recent meta-analysis reporting large overall effects (Morina et al., 2017). Memory rescripting has not been routinely viewed as a reconsolidation procedure. Accordingly, conceptualizing it in this fashion may encourage strategic modifications in the timing of procedures to better harness reconsolidation effects to potentially improve outcomes.

Sleep: As with consolidation, sleep also plays a role in memory reconsolidation. Neuroimaging studies suggest that memories are "replayed" during sleep, a process that potentially supports reconsolidation (for review, see Stickgold & Walker, 2007). Although studies have demonstrated sleep dependent reconsolidation of procedural memories in humans (for review, see Stickgold & Walker, 2007), very little research has explored whether sleep facilitates the reconsolidation of fear memories. Rolls and associates (2013) examined this question by fear conditioning mice to an odor, and 1 day later, presenting the odor cue, then administering a protein synthesis inhibitor while the mice were asleep. Consistent with pharmacological reconsolidation interference studies conducted during waking, they found that fear memories were attenuated by this procedure. It is yet to be determined, however, whether interfering with reconsolidation during sleep is more effective than during waking hours.

Brain stimulation and neuromodulation: A couple studies have attempted to interfere with the reconsolidation of conditioned fear memories in humans using brain stimulation and neuromodulation after memory retrieval. One study delivered tDCS to the right prefrontal – anodal and left supraorbital – cathodal regions after retrieval and found enhanced reconsolidation (Mungee et al., 2014). A follow up study examined tDCS delivered in the opposite manner (right prefrontal—cathodal, left supraorbital— anodal) in attempt to find an interference effect but found no effect (Mungee, Burger, & Bajbouj, 2016). Research with TMS has been somewhat more promising. A study (Isserles et al., 2013) explored the effectiveness of deep TMS to the medial PFC following brief exposure to trauma memories in treatment-resistant PTSD patients. The result was significantly greater improvements in CAPS intrusive symptoms in the TMS group. Although the mechanism at play is unclear, the investigators hypothesized that TMS interfered with the reconsolidation of the trauma memories, rather than enhancing extinction learning. Electroconvulsive therapy (ECT) after memory retrieval has also been used as a reconsolidation-blockade strategy. This strategy has shown success for interfering with the retention of recent learning in depressed patients undergoing ECT (Kroes et al., 2014), but, to our knowledge, has not been applied to clinically-relevant memories. Finally, although there appears to be promise in animal models for influencing the valence of fear memories via direct brain stimulation through optogenetics (Redondo et al., 2014), a safe way to apply optogenetics to humans has yet to be discovered.

Limitations of strategies targeting memory reconsolidation—Some researchers have questioned whether there are limitations or boundary conditions to reconsolidation

interference (Auber, Tedesco, Jones, Monfils, & Chiamulera, 2013). Specifically, it has been shown that even with pharmacological reconsolidation blockade, new learning must take place during the reconsolidation window for interference to occur (Sevenster et al., 2012). Additionally, researchers have questioned whether older, stronger, and hippocampal-dependent memories are less susceptible to reconsolidation interference effects (Auber et al., 2013; Kredlow et al., 2016). Individual studies have surpassed these boundary conditions, with one potential strategy being to epigenetically prime the expression of neuroplasticity-related genes (Gräff et al., 2014). However, additional research is needed to elucidate how these boundary conditions may impact the translation of these strategies to the clinic.

3. Enhancing Memories of Therapeutic Learning

Instead of influencing the memories that underlie psychological disorders, other strategies have focused on enhancing the consolidation of memories of therapeutic learning in the treatment of psychological disorders. These strategies involve new learning and the assimilation of that learning into existing memory structures. Researchers have investigated pharmacological and behavioral strategies to achieve this end. Many of these strategies have been researched in the context of exposure therapy for anxiety and traumatic stress disorders but have potential applications for non-exposure based psychotherapies and other psychological disorders.

Pharmacological strategies—Results of studies combining traditional pharmacotherapy with psychotherapy for the treatment of anxiety and traumatic stress disorders have been generally disappointing (Otto et al., 2010), leading researchers to explore novel agents targeting memory for psychotherapeutic learning, rather than anxiety symptoms directly (Otto et al., 2016a).

D-cycloserine (DCS): Research on DCS is the furthest along with regards to translation to the clinic. DCS, a partial agonist of the N-methyl-d-aspartate glutamatergic receptor, has been shown to aid in the consolidation of extinction learning in animal models and human clinical applications (Norberg, Krystal, & Tolin, 2008). Multiple meta-analyses have documented the overall positive effect of DCS augmentation of exposure therapy for anxiety disorders (e.g., McGuire, Wu, Piacentini, McCracken, & Storch, 2016; Norberg et al., 2008). Variations in the magnitude of effect sizes across studies and across meta-analyses, as well as some negative findings in particular disorders (e.g., PTSD: Litz et al., 2012), have led researchers to explore moderators of these effects and question the optimal method of applying DCS to enhance consolidation of therapeutic learning (Otto et al., 2016a). In these clinical studies, DCS is typically administered orally pre-treatment so that it can reach near-peak levels in the brain by the conclusion of the exposure session. However, there is evidence that DCS should be given only around successful exposure sessions given its apparent ability to strengthen memory regardless of exposure outcome (Smits et al., 2013a, b). This finding has led researchers to pursue ongoing investigations of whether post-session administration of DCS, contingent on the success of the exposure, can further enhance outcome for this augmentation strategy (Hofmann et al., 2015). In addition to being explored as a method to enhance exposure therapy (Otto et al., 2016a) across the anxiety disorders, OCD, PTSD, addictions, and anorexia nervosa, DCS is also being explored as a method to

enhance consolidation of non-extinction based declarative learning that takes place during cognitive-behavioral therapy for depression (Otto et al., 2016b) and cognitive remediation for schizophrenia (Otto et al., 2016a).

Cortisol: Research suggests that cortisol can also be applied to enhance the consolidation of fear extinction learning in animals (Yang, Chao, & Lu, 2006). This strategy has been translated to patients with anxiety disorders. De Quervain and colleagues (2011) augmented exposure therapy for specific phobia with cortisol and found that it resulted in significantly greater reductions in physiological responses during exposures and post-treatment self-reported fear. This strategy has been replicated with anxiety and PTSD (for review, see de Quervain et al., 2017) but is yet to be examined in other disorders.

Methylene blue: Methylene blue is a non-neuroleptic phenothiazine which in low doses enhances memory consolidation through improving oxidative energy metabolism in the brain (Gonzalez-Lima & Bruchey, 2004). After animal studies demonstrated improved retention of conditioned fear extinction with post-training administration of methylene blue (e.g., Gonzalez-Lima & Bruchey, 2004), Telch and colleagues (2014) explored the use of methylene blue to augment exposure therapy for claustrophobia. Consistent with findings regarding DCS, Telch and colleagues (2014) found that methylene blue promoted the retention of fear extinction for individuals who evidenced successful extinction during exposure sessions. This strategy has yet to be explored to augment exposure therapy for other disorders.

Yohimbine: Yohimbine is a selective competitive alpha2-adrenergic receptor agonist that increases extracellular norepinephrine. Research has shown that post-learning adrenergic stimulation enhances memory consolidation in animals and humans (McGaugh, 2000). However, animal studies of the use of yohimbine to enhance extinction memory consolidation have been mixed (for review, see Fitzgerald, Seemann, & Maren, 2014). Similarly, the few studies that have examined yohimbine to augment exposure therapy in humans have also been mixed (Meyerbroeker, Powers, Van Stegeren, & Emmelkamp, 2011; Powers, Smits, Otto, Sanders, & Emmelkamp, 2009; Smits et al., 2014). Powers and colleagues (2009) found that adults with claustrophobia who received exposure therapy augmented by yohimbine versus placebo, demonstrated greater improvement in fear ratings during exposures and better outcomes in claustrophobia severity at post-treatment and follow up. Similarly, Smits and colleagues (2014) found faster improvement and better outcomes with yohimbine augmentation of exposure therapy for social anxiety disorder. Meyerbroeker and colleagues (2011), however, did not find faster improvement or better outcomes with yohimbine augmentation of exposure therapy for flying phobia. A trial is currently underway examining enhancement of prolonged exposure therapy for PTSD with yohimbine (Wangelin, Powers, Smits, & Tuerk, 2013).

Modafinil: Modafinil is a wake promoting agent typically used to treat daytime sleepiness. It is a psychostimulant that amplifies the release of glutamate and serotonin and inhibits the release of GABA (Minzenberg & Carter, 2008). In animal studies, modafinil has been shown to improve performance on learning and memory tasks and enhance fear conditioning when

given at a low dose (e.g., Shuman, Wood, & Anagnostaras, 2009). In humans, modafinil may prove to be useful in enhancing extinction learning or non-fear based declarative learning, but validation of this approach with patients is pending (Otto et al., 2016b). Modafinil is also being explored as an augmentation strategy for cue-exposure therapy for addiction. However, it is unclear whether effects are due to enhanced extinction learning or more direct effects on craving (Nuijten, Blanken, Van den Brink, Goudriaan, & Hendriks, 2016).

Other agents: Other pharmacological agents being explored include cannabidoil (Jurkus et al., 2016) and oxytocin (Acheson, Feifel, Kamenski, Mckinney, & Risbrough, 2015).

Cognitive and behavioral strategies

Cognitive strategies: In an article on the importance of memory enhancement strategies for clinical practice, Otto (2000) underscored the memory challenges brought by weekly 50 minute sessions that "account for less than 1% of the average outpatient's waking hours" (p. 166). To address this challenge, Otto (2000) discussed the importance of providing information in a useful and engaging way, emphasizing the role of vivid imagery, stories and guiding metaphors to enhance retention of therapeutic principles. More recently, Harvey et al. (2014) has similarly recommended the use of "Memory Support" strategies to improve outcomes from psychosocial treatment, and reminded clinicians that memory deficits are common across mental health disorders and have an impact on the efficacy of interventions (for review, see Moshier, Calkins, Kredlow, & Otto, 2015). Harvey and associates (2014) recommend the use of a number of cognitive strategies to enhance memory (e.g., use of cue based reminders, repetition, rehearsals, and praising of recall) in or between sessions. Some of these strategies take advantage of rapid schema consolidation described above. These strategies are already part of many cognitive-behavioral approaches to treatment, but additional memory support interventions have the potential to improve upon these standard strategies (Dong, Lee, & Harvey, 2017).

An alternative approach focuses on enhancing the specificity of autobiographical memories, as a strategy to counteract the over-generality of memories associated with depression and other emotional disorders (Sumner, Griffith, & Mineka, 2010). For example, Memory Specificity Training (Raes, Williams, & Hermans, 2009) aims to enhance the specificity of emotional memory recall by training individuals to recall specific positive, negative, and neutral memories in the context of a four-session intervention, potentially enhancing the ability to use episodic memories in social or interpersonal problem solving, imagining one's future, or inhibiting rumination. Initial trials of these and related training methods indicate benefit in the range of a small to medium effect size for the treatment of depression (Hitchcock, Werner-Seidler, Blackwell, & Dalgleish, 2016).

Mindfulness is also used as a strategy to change one's relationship with memories that underlie psychological disorders and may also impact memory biases. Mindfulness has been shown to decrease overgeneralized negative autobiographical memories and increase memory specificity (Heeren, Van Broeck, & Philippot, 2009). Other studies have shown that mindfulness can enhance recall for positively-valenced stimuli (Roberts-Wolfe, Sacchet, Hastings, Roth, & Britton, 2012). Finally, because mindfulness can enhance attention,

working memory, and executive functioning and may also specifically enhance inhibitory learning (Chiesa, Calati, & Serretti, 2011; Treanor, 2011), mindfulness training has the potential to enhance an individual's ability to learn and remember therapeutic content.

Inhibitory learning approach: Similarly, although inhibitory learning is often already present in cognitive-behavioral treatments, Craske, Treanor, Conway, Zbozinek, and Vervliet (2014) propose that strategies directly targeted towards enhancing inhibitory learning will enhance memory for exposure therapy. Inhibitory learning is the safety learning that occurs during extinction – learning that the conditioned stimulus no longer predicts the unconditioned stimulus. Craske and colleagues' (2014) recommended strategies to enhance inhibitory learning include: (1) designing exposures to maximize violation of expectancies, (2) conducting exposure to multiple feared conditioned stimuli individually and in concert, (3) occasionally reinforcing a conditioned stimulus with an unconditioned stimulus during extinction training, (4) removal of safety signals or safety behaviors, (5) stimulus variability throughout exposure, (6) utilizing retrieval cues during extinction training to then be used in other contexts once extinction is over to aid in the retrieval of extinction memory, and (7) conducting exposure in multiple contexts. Although the inhibitory learning approach was formulated with exposure therapy for anxiety disorders in mind, it may be relevant to other types of learning, particularly appetitive learning. For example, the use of retrieval cues has also been applied to enhance appetitive extinction memory retrieval in the treatment of substance use disorders (e.g., Rosenthal & Kutlu, 2014).

Sleep: As described above, sleep plays a crucial role in memory consolidation and assimilation (Landmann et al., 2014) and thus, can also be harnessed to enhance consolidation of therapeutic learning. Pace-Schott et al. (2009) demonstrated that sleep following fear extinction promoted the generalization of extinction learning in humans. Similarly, they found that sleep following exposure therapy for spider phobia led to better extinction retention and generalization (Pace-Schott, Verga, Bennett, & Spencer, 2012). These findings were replicated in another study that administered naps following exposure therapy for spider phobia (Kleim et al., 2014) and this strategy is currently being examined in a larger trial with social anxiety disorder (NCT02325128). In addition, sleep quality has been linked to exposure therapy outcomes in the context of a clinical trial for social anxiety disorder. Specifically, better sleep quality predicted greater anxiety reduction from one session to another and over the course of treatment more generally (Zalta et al., 2013). Accordingly, prescribing naps after successful therapy sessions or intervening on poor sleep quality more generally may be valuable strategies for enhancing therapeutic learning.

Physical activity: A wealth of research indicates that physical activity can act as a cognitive enhancer (e.g., Firth et al., 2016), with evidence that the mechanism behind these effects is an increase in brain derived neurotropic factor (BDNF) that reliably results from exercise (Szuhany, Bugatti, & Otto, 2015). Physical activity has been applied to enhance therapeutic learning in the treatment of both fear-based and other disorders. For example, physical activity immediately before or after fear extinction has been shown to enhance extinction learning in animals (Siette, Reichelt, & Westbrook, 2014). Likewise, Powers et al. (2015) found that physical activity prior to prolonged exposure led to greater improvement in PTSD

symptoms and elevated BDNF relative to the effects of prolonged exposure alone. As physical activity has direct benefits for reducing anxiety (Asmundson et al., 2013), it is unclear whether the mechanism in this study was enhanced consolidation of extinction learning or enhanced anxiety reduction. In a different application, Malchow and associates (2015) found that the addition of physical activity increased the effects of computer-assisted cognitive remediation training on global functioning and specific cognitive tasks in schizophrenia patients. There is some evidence that the benefits of combining physical activity with cognitive remediation operate by separate rather than synergistic mechanisms (Suo et al., 2016). Accordingly, physical activity appears to function as a broad-based cognitive enhancer, with promising early results for its combination with specific clinical interventions.

The issue of timing and intensity of exercise deserves particular attention. There is a caution in the literature that exercise immediately after learning may result in too much neurogenesis in the hippocampus, which in turn may lead to forgetting (Akers et al., 2014). Promoting neurogenesis typically facilitates the formation of new hippocampal memories, facilitating learning. However, as new neurons integrate into the hippocampus, they form new synaptic connections that may compete with existing older synaptic connections. A high level of neurogenesis may result in complete remodeling of the synaptic connections, and thus forgetting of older memories. Akers et al. (2014) explored this hypothesis by training adult mice in contextual fear conditioning then utilizing physical activity to induce neurogenesis immediately after training; this specific protocol was associated with *reduced* contextual fear memory when mice were tested 6 weeks later. In this case, exercise potentially interfered with the consolidation of the contextual fear memory. This research suggests that exercise immediately after extinction learning could also potentially interfere with rather than enhance extinction learning as suggested by Siette et al. (2014). Further research should explore what intensity of physical activity and timing of administration best supports enhanced consolidation of therapeutic interventions.

Brain stimulation and neuromodulation: Recently, there has also been an increasing interest in the use of brain stimulation to enhance connectivity of brain regions that may be involved in extinction memory consolidation processes. Animal research indicates that deep brain stimulation, vagus nerve stimulation, and TMS can be used to enhance extinction learning (for review, see Marin, Camprodon, Dougherty, & Milad, 2014). A few studies have translated this work to human clinical samples. Given the prominent role of the PFC in extinction learning, Osuch and associates (2009) examined repeated TMS to the dorsolateral PFC combined with exposure therapy for PTSD, and found larger improvement in hyperarousal symptoms relative to exposure alone. TMS is also being explored as a method to enhance cognitive-behavioral therapy for anxiety disorders (Herrmann et al., 2016) and depression (D'Urso, Mantovani, Micillo, Priori, & Muscettola, 2013). Researchers have also started to explore tDCS as a method to enhance extinction learning. Van't Wout and colleagues (2016) found that administering tDCS to the ventromedial PFC during the first block of extinction led to accelerated learning during the second block of extinction. However, this strategy is yet to be examined in clinical populations.

Conclusions and Clinical Caveats

A collection of new strategies for enhancing psychosocial treatment now appear to be at hand. These strategies are directed toward strengthening the therapeutic learning that occurs in psychosocial treatment sessions, aiding both the retention and utilization of new information, while also speeding the degree to which new information updates or replaces older maladaptive memories. The success of these varied strategies has the potential to further ease suffering and accelerate the progress of patients toward recovery. Yet these advances are not arriving without some important clinical cautions that take the general form of "be careful what you enhance." Stated differently, when memory for session content is strengthened, it becomes increasingly important to offer especially targeted and efficacious treatment.

This caveat has been demonstrated convincingly in the pharmacologic augmentation literature for exposure-based cognitive-behavioral therapy for anxiety disorders. Specifically, in an initial study, Smits and associates (2013a) found exposure-enhancement with DCS offered an advantage only for individuals who achieved low-fear by the conclusion of an exposure session. Moreover, in a larger trial, Smits and associates (2013b) replicated this finding but also found that an opposite effect was evident for those with high-fear at the end of exposure. For the latter individuals, DCS augmentation appeared to slow therapeutic learning relative to placebo augmentation. In other words, exposure enhancement from DCS appeared to make good exposure therapy better and bad exposure therapy worse. This effect has also been replicated for other putative memory enhancers including yohimbine (Smits et al., 2014) and methylene blue (Telch et al., 2014). Accordingly, it appears that memory enhancement strategies have intensified rather than attenuated the need for well-honed psychosocial interventions.

Moreover, as evidence builds on the ability to utilize reconsolidation effects to alter original fear memories, there is an increasing rationale for caution around suggesting memory content to patients once older memories have been primed. This issue has already received attention in the false memory literature (e.g., Loftus & Polage, 1999), but the elucidation of reconsolidation procedures underscores the ease by which specific suggestions of novel content or inaccurate narratives might be integrated into an individual's memory. As such, with procedures such as post-retrieval extinction, we may see a similar pattern in that benefits may depend on the success of extinction during the reconsolidation window.

These cautions do not detract from the potential benefits that advances in memory research are offering to clinical care. For example, again using DCS enhancement of anxiety and related disorders as a model, benefit has been the general rule for patients in clinical trials of this augmentation strategy. Nonetheless, attention to the quality of individual exposure sessions has the potential to further enhance these findings (Otto et al., 2016a), while slowing adoption of DCS enhancement around cases or conditions where exposure quality is harder to manage (e.g., Litz et al., 2012). This approach may also be useful for other memory consolidation enhancement strategies (e.g., sleep, physical activity, or brain stimulation), applying these strategies judiciously to only the most effective sessions of psychotherapy.

Future Directions

The literature presented in this review sheds light on many new directions for future research. The first clear direction involves pushing successful strategies further along the line of translation from animal to human laboratory studies, from human laboratory to clinical pilot trials, and finally from pilot to randomized controlled trials. Many of the strategies described have not yet been examined in patients and given promising results with non-clinical samples, warrant further exploration. The second direction for future research involves the application of the current strategies to different types of memories and disorder categories. In particular, most strategies to interfere with memory reconsolidation and enhance the consolidation of therapeutic learning have yet to be tested with declarative memories/learning and applied to non-fear-based disorders. A third direction for future research involves the further exploration of whether strategies that are currently used in one domain could potentially be applied to another. As elucidated above, many strategies that are used to interfere with consolidation have also been used to interfere with reconsolidation (e.g., propranolol) and similarly, strategies used to interfere with consolidation have also been harnessed in different ways to enhance consolidation (e.g., sleep). Further cross-pollination of these strategies may lead to fruitful avenues of research. Lastly, there is ample room for examination of moderators associated with these effects. Identifying moderators may allow for the examination of more nuanced applications of these strategies, such as in the case of post-administration of DCS. Specific to fear-based disorders, understanding of whether these strategies impact cortical or subcortical circuits of threat responding (LeDoux & Pine, 2016) may also allow for more targeted application. Our hope is that these new directions of research are aided by Supplementary Table 1.

In sum, the translational research agenda for memory enhancement and modification is enjoying a period of particular growth and success. This success bodes well for introducing a number of novel strategies into clinical practice that can help extend the reach and benefits of empirically-supported psychosocial treatments. For clinicians, this review encourages ongoing consideration of how to make interventions both salient and memorable for use. For researchers, this review encourages the translation of strategies that have proven effective in animals to humans and further to clinical applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies