6

Emotion–Memory Interactions

Implications for the Reconsolidation of Negative Memories

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Introduction

Emotion has the power to shape how we learn about and remember information, including important life events. Among the most widely accepted principles and replicated findings in psychological research is that emotional events are better remembered with more vividness and higher confidence than mundane or trivial everyday events. Emotional memories can also be defined by their persistence and a fierce resistance to being forgotten over time. That emotional experiences have a privileged status in long-term memory is adaptive insofar as it helps ensure that we remember people, places, stimuli, and situations associated with highly meaningful experiences. This feature can present a burden, however, when unwanted memories are intrusive and disrupt everyday life. Persistent negative memories occur in a number of mental health disorders, but are perhaps best exemplified in posttraumatic stress disorder (PTSD), for which intrusive memories of trauma (or multiple traumas) can seem unceasing (Brewin & Holmes, 2003).

A great deal of laboratory research in psychology and neuroscience has uncovered neurobehavioral mechanisms involved in the prioritization of emotional experiences in humans and other animals (LaBar & Cabeza, 2006; McGaugh, 2015). Much of the early neuroscience work on what we might today consider emotion research was originally motivated by trying to achieve an understanding of basic learning and memory processes in the mammalian brain. Emotional arousal, like that induced by an electrical shock, just so happens to be a highly effective way to generate measurable behavior and a long-term memory in a laboratory setting. Much contemporary research on emotional memory is now motivated in large measure by the clinical implications of this work. Specifically, there is a strong interest in understanding how emotional

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memories can be diminished or controlled by new corrective experiences, pharmacological interventions, or a combination of behavioral and pharmacological approaches (Dunsmoor, Niv, Daw, & Phelps, 2015; Parsons & Ressler, 2013). Recent advances in human neuroimaging now allows researchers to extend neuroanatomical knowledge of how emotion shapes learning and memory from laboratory animals to humans, with the ultimate hope that this knowledge will contribute to more effective treatments for a host of mental health disorders.

The goal of this chapter is to detail key historical and emerging trends in the neuroscience of emotional memory with an emphasis on how this knowledge is being used to help weaken the effect of unwanted emotional memories in humans. The chapter is divided between the two predominant avenues of research on emotional memory: episodic memory, which relies on the hippocampus, and conditioned learning, which relies on the amygdala. Episodic and conditioned memory are typically investigated independently within largely separated academic fields. However, research on both episodic memory and fear conditioning offer important insights and unique advantages toward understanding how emotion affects learning and memory. An understanding of emotional memory therefore warrants consideration of both avenues of psychological research, and the translation of this knowledge to the clinic will ultimately benefit by an integration across these domains.

How Emotion Shapes Episodic Memory

Emotionally charged experiences gain privileged access to long-term memory, sometimes referred to as the emotional enhancement of memory. Importantly, emotion can have widespread effects across a variety of different "types" of memory, which can be coarsely divided between explicit and implicit memory (see Chapter 2 of this volume). Explicit (or declarative) memory typically refers to those memories that can be consciously accessed and retrieved and can be further subdivided into memories for particular events or "episodes" (episodic memory), specific life events (autobiographical memory), and general knowledge (semantic memory). In contrast, implicit (or nondeclarative) memory typically refers to those memories that can be acquired and retrieved independent of conscious awareness, but that can still be evaluated through observable behavior. Implicit memories include skills, priming, non-associative learning, and conditioning. The proceeding section on fear conditioning deals with implicit emotional memories (see Chapter 10 of this volume; see also Debiec chapter).

Attentional Focusing and Memory Trade-Offs for Emotional Details

Much of the emotional memory research in humans has focused on episodic memories for visual scenes that contain both emotional and neutral elements. One fundamental question from early research on emotional memories was whether certain details of an emotional episode are selectively remembered at the expense of other details encoded at the same time. Early studies showed that people tend to have better memory for the content of emotional scenes that are central and command the most attention, while peripheral, background, or emotionally irrelevant information are poorly remembered (Easterbrook, 1959). This trade-off in memory tends to be enhanced for negative versus positive scenes (Bennion, Ford, Murray, & Kensinger, 2013) and is best exemplified by the weapon focus effect (Loftus, 1979), wherein people focus on the most emotional aspect of an event (a gun pointing directly at you) and have poorer memory for surrounding details (the identity of the assailant holding the gun). Phenomena such as weapon focus have obvious implications for eyewitness testimony, since a witness to a crime may have unreliable memory for peripheral details that would help identify the criminal.

A simple explanation for the memory trade-off for central emotional versus peripheral or background neutral details is that people spend longer attending to the emotional details at the time of encoding. However, Steintzman and Kensinger (2013) measured eye-tracking during emotional encoding and found that, on average, people do not spend substantially more time focused on the emotional details. Thus, the memory trade-off effect is perhaps a result of selective preservation of emotional details and/or a diminution in memory for the surrounding neutral details over a period of consolidation. Payne, Stickgold, Swanberg, and Kensinger (2008) have shown that the emotional aspects of a scene are selectively retained in memory after a period of sleep, supporting a role for postencoding processes on emotional memory trade-offs.

Overconfidence in Emotional Memories

Emotional memories are not only better remembered, but they are often remembered with a high degree of subjective confidence that the event occurred just the way it is remembered (Hirst & Phelps, 2016). Consider for example the memory of a highly emotional event like September 11, 2001. Nearly anyone old enough to remember 9/11 can describe a number of details from that day: where you were, who you were with, etc. When recounting these details, the memories are much easier to retrieve, and belief in the accuracy of the memory for these details

is much stronger than for details from the days before or after 9/11. However, the ease with which these memories are accessed and retrieved belies an important fact—memory is not a veridical (entirely accurate) account of what took place in the past. Instead, memories change over time based on subsequent experiences and the present circumstances surrounding memory retrieval. What are often called "flashbulb" memories are not mental photographs of the past.

In the days after 9/11, a consortium of memory researchers compiled a survey to assess people's memory for certain details from that tragic day (Hirst et al., 2009). Some details were consistent with the emotional flashbulb qualities of the memory (Where were you? Who were you with?), and other details assessed fact-based memories for the day that did not involve the personal details (What airlines were hijacked? Where was President Bush when the planes hit the World Trade Center?). Participants then filled out similar surveys 11 months, 35 months, and 10 years (Hirst et al., 2015) later to assess consistency in their memory over time. Despite the high degree of emotion ascribed to flashbulb memories, people showed abrupt forgetting of these personal details after 1 year, but maintained a high degree of confidence in their memory. Between the first, third, and tenth year after 9/11, the amount people remembered stabilized.

In laboratory studies, emotion enhances both accuracy and confidence, with a potentially disproportionate impact on confidence over accuracy. An argument can be made that the weighting of confidence over accuracy confers an evolutionary advantage (Phelps & Sharot, 2008). That is, it may be more important to have confidence when retrieving certain emotional memories to quickly act upon that knowledge. For example, as opposed to being unsure whether or not this is the precise location where you recently encountered a ferocious predator, it is more advantageous to behave as if it is and avoid that location altogether. In other words, better safe than sorry. A trade-off between accuracy and confidence could arguably be beneficial in future situations when the decision to rapidly act upon our past experience is a matter of survival. Of course, the tendency to be overconfident in our memory is more often brought to bear on less critical matters.

The Neural Correlates of Emotional Episodic Memory

Numerous neurobiological studies with laboratory animals over the past several decades have revealed how arousal at the time of encoding, or soon after encoding, can strengthen memory through a cascade of endogenous neurohormone activations (McGaugh, 2004). Much of this research centers on the role of the basolateral amygdala in *modulating* memory consolidation via widespread projections with a host of brain regions involved in multiple forms of memory

(Cahill & McGaugh, 1998;see Figure 6.1). For instance, projections from the basolateral amygdala to the hippocampal complex are important for memories involving contexts, spatial learning, and other episodic-like experiences (e.g., object recognition) in animals. Increasing or decreasing amygdala activity has corresponding effects on several types of long-term memory (McGaugh, 2015). For example, posttraining administration of noradrenaline to the basolateral amygdala enhances long-term performance for hippocampus-dependent learning tasks, like object recognition or maze learning, whereas adrenergic antagonists impair performance. Endogenous release of stress hormones during or after training can also drive memory modulation. While not discussed here, the reader is directed to a number of comprehensive reviews on the role of stress hormones on learning and memory (Raio & Phelps, 2015; Rodrigues, LeDoux, & Sapolsky, 2009; Schwabe & Wolf, 2013; Wolf, Atsak, de Quervain, Roozendaal, & Wingenfeld, 2015). Finally, neuromodulation of the amygdala and hippocampus also modulate the retrieval of long-term emotional episodic-like memories (Roozendaal, McEwen, & Chattarji, 2009).

To investigate the neural correlates of human episodic memory using functional magnetic resonance imaging (MRI), analyses often focus on encoding

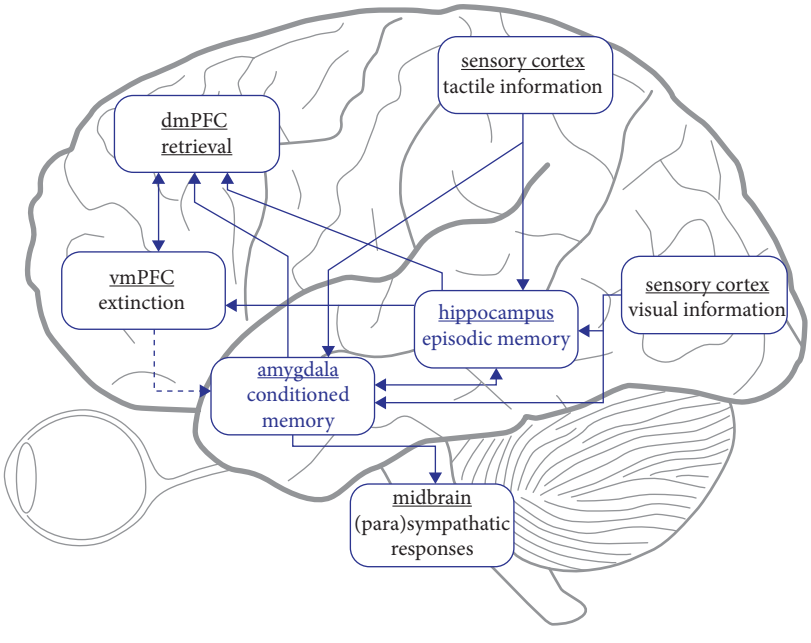

Figure 6.1 Simplified neural model illustrating how connections between the amygdala, hippocampus, and cortex modulates implicit and explicit emotional memories.

related activity for subsequently remembered versus forgotten stimuli. This "difference in memory" reveals that hippocampal activity at encoding is correlated with subsequently remembered information (Wagner et al., 1998). These neuroimaging studies were presaged by research in amnesic patients with damage to the medial temporal lobe (Milner, Squire, & Kandel, 1998; also see Chapter 2 of this volume). The amygdala, in contrast, is associated with encoding related success for emotional versus neutral information (Dolcos, LaBar, & Cabeza, 2004). These neuroimaging findings were also presaged by early studies in patients with rare bilateral lesions to the amygdala from Urbach–Wiethe disease who have selective deficits in emotional enhancement of episodic memory (Adolphs, Cahill, Schul, & Babinsky, 1997; LaBar & Phelps, 1998; Markowitsch et al., 1994). Functional activation and connectivity analyses indicate that the amygdala upregulates hippocampal processing, via a beta-adrenergic mechanism, during acquisition and consolidation to enhance episodic memory for emotional events (de Voogd, Klumpers, Fernández, & Hermans, 2017; Dolcos et al., 2004; Richardson, Strange, & Dolan, 2004), consistent with animal models proposing a modulatory role of the amygdala in influencing hippocampal processing (McGaugh, 2004). In line with this idea, a functional MRI (fMRI) study with patients revealed that hippocampal pathology predicts subsequent episodic memory for both neutral and emotional events, whereas amygdala pathology predicts episodic memory for emotional events only (Richardson et al., 2004). Furthermore, amygdala pathology correlated with hippocampal encoding-related activity while hippocampal pathology correlated with encoding-related amygdala activity for subsequently remembered emotional events. A host of other brain regions are consistently implicated in emotional memory encoding during human neuroimaging as well, including sensory regions, prefrontal cortex, the insula, and the parietal cortex (Murty, Ritchey, Adcock, & LaBar, 2010). This amygdala–hippocampus network is also involved during retrieval of emotional episodic memories (Dominique, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kroes, Strange, & Dolan, 2010; Takashima, van der Ven, Kroes, & Fernández, 2016). In sum, both studies in laboratory animals and humans suggest that the amygdala upregulates processing in the hippocampus and other neural regions via neuromodulatory mechanisms during encoding, consolidation, and retrieval to enhance episodic memory for emotional events.

Emotion Can Color Memory for Simultaneous Neutral Events

One reason emotional events are better remembered could be due to the intrinsic features of emotional stimuli. As compared to neutral material, emotional stimuli tend to be more complex, engaging and novel and consist of a limited

range of semantic or thematic content (e.g., disgust or violent objects or scenes, as opposed to any number of neutral objects or scenes; Talmi, 2013). Disentangling selective attention toward these intrinsic features from selective memory processes, per se, is a challenge in memory research. That is, the attention grabbing features of an emotional stimulus ensure that neural and behavioral systems involved in detecting and reacting to salient stimuli, like the amygdala and sensory cortex, are engaged. These regions are also involved in modulating long-term episodic memory, creating a potential confound in ascribing separate roles for encoding processes versus modulation of postencoding consolidation, storage, or retrieval.

A fundamental question therefore is what role emotion, and not attention per se, has on enhancing episodic memory. To answer this question, Cahill and McGaugh (1995) had participants learn a story consisting of photographic images and an auditory narrative. For half the participants, the auditory narrative was neutral while for the other half the narrative was emotional. Although all participants saw the exact same images, the participants who had heard the emotional narrative remembered the details of the images better. This indicates that emotion modulates how neutral information is encoded.

In a related line of research, participants encode neutral items that are presented superimposed on a neutral or emotional scene (i.e., a context; Maratos, Dolan, Morris, Henson, & Rugg, 2001; Smith, Dolan, & Rugg, 2004; Smith, Stephan, Rugg, & Dolan, 2006). At a retrieval test without the scenes, memory is better for neutral items that had been encoded on an emotional versus neutral background. This emotional enhancement of neutral episodic memory is associated with increased amygdala–hippocampal activity and connectivity during encoding and retrieval (Maratos et al., 2001; Smith et al., 2004, 2006). Further, activity at encoding is associated both with the accuracy of the retrieval of the emotional context and confidence in retrieving an emotional context (Takashima et al., 2016). Thus emotion can enhance episodic memory for simultaneously encoded neutral information independent of emotional features of a retrieval cue modulating memory.

Emotion Can Color Memory for Subsequent Neutral Events

As previously discussed, the emotional enhancement of episodic memory cannot merely be explained by emotional features of a cue enhancing a retrieval process. However, the previously mentioned studies do not exclude the possibility that attention-grabbing features of an emotional stimulus at the time of encoding determine the subsequent enhancement of episodic memory for neutral events. Importantly, emotion also has the power to shape memory for neutral events in

the moments following an arousing event. This offers a novel way to study the effect of emotion on memory by circumventing the intrinsic features of emotional stimuli. As a real-world example, consider the details remembered from an emotional event like an automobile accident. The most intense component of that experience is likely to be the moment of impact and the immediate feelings of shock and pain. But the long-term memory for that event contains a host of details from the minutes to hours afterward that are not intrinsically emotional. For instance, you might have a stronger than normal memory for the places you went and who you were with later that day.

In a recent study, Tambini, Rimmele, Phelps, and Davachi (2017) asked whether patterns of brain activity related to encoding a set of emotional stimuli carry forward in time to affect memory encoding for subsequently presented neutral stimuli. During fMRI, subjects viewed a block of emotional and neutral pictures. Half the subjects viewed the neutral pictures in the first block and the emotional pictures second; the other half of subjects had the order of neutral and emotional blocks reversed. Memory was then tested for all the pictures 6 hours later in a surprise memory test outside the scanner. For subjects who viewed the neutral pictures first, memory was greater for the subsequently presented emotional pictures, in line with an expected enhancement of memory for emotional versus neutral items. However, for subjects who viewed the neutral pictures *after* the emotional pictures, memory was equivalently high for both emotional and neutral pictures. Furthermore, the pattern of brain fluctuations identified during the viewing of emotional stimuli was reinstated ~10 to 30 minutes later when subjects viewed neutral stimuli. This reinstatement of brain activity from one viewing block to the next did not occur if neutral images were viewed first, suggesting a carry-forward effect that biased how subsequent neutral information is encoded.

Emotion Can Color Memory for Past Neutral Events

Emotion not only has the ability to shape memory for the present and the future but can also modify what information is remembered from before an emotional event occurred. This retrograde (or retroactive) effect of emotion is exemplified by the content of persistent and intrusive memories following trauma. For instance, Ehlers et al. (2002) analyzed the content of intrusive memories in PTSD and showed that many of these details consist of seemingly trivial or neutral stimuli or situations that were temporally associated with the traumatic event. For instance, a patient who had been in a severe automobile accident had intrusive memories of oncoming headlights, and a victim of rape had intrusive memories of the sight of the man standing in a hallway as he had appeared

before the assault. Ehlers and colleagues refer to these memories as "warning signals" that the brain will later interpret as signs of impending threat. In this way, strong memories for neutral events or stimuli act as conditioned stimuli (CSs) in Pavlovian conditioning, which serve to produce a conditioned threat response in anticipation of an impending aversive unconditioned stimulus (US). Intriguingly, memories for these intrinsically neutral details may be more intrusive than details of the actual trauma. Indeed, memory of a trauma might be disorganized, and in rare cases, there is reported psychogenic or dissociative amnesia for the trauma itself and events preceding its occurrence (Jaffe, 1968; Loftus & Burns, 1982; but also see Merckelbach, Dekkers, Wessel, & Roefs, 2003).

In the laboratory, a number of factors can determine whether emotion leads to an enhancement or a diminishment of memory for preceding neutral events. Strange, Hurlemann, and Dolan (2003) showed that neutral items are *poorly* remembered if they precede an emotional picture, an effect they refer to as emotion-induced retrograde amnesia, which depends on the amygdala and noradrenaline (Hurlemann et al., 2005; Strange, Kroes, Fan, & Dolan, 2010; Strange, Kroes, Roiser, Tan, & Dolan, 2008). In a conflicting finding, Anderson, Wais, and Gabrieli (2006) showed that neutral pictures are *better* remembered a week later if they precede an emotional picture by 4 seconds, but not 9 seconds. In attempting to reconcile these findings, Mather and colleagues (Knight & Mather, 2009; Mather & Sutherland, 2011) developed the arousal-biased-competition (ABC) model, which proposes that arousal benefits encoding of prioritized information, but diminishes processing of low-priority information. Priority can take the form of attentional allocation, such that the subjects' top–down or bottom–up attention is drawn to the neutral information in the moments before, during, or after an emotional stimulus.

Emotional experiences also have the ability to reach further back in time and enhance memory for neutral details encoded several minutes before the emotional event. Again, consider the morning of 9/11. If you heard the news in the morning soon after the first plane struck the World Trade Center, then there is a strong chance you did not yet realize the significance of the disaster. As events unfolded, the impact of what happened began to come into focus. And yet, some of the details we still remember from that day begin before that moment of realization. For example, we might still remember hearing the first vague report of a plane flying into a building, our initial thoughts ("a pilot probably just lost control of their single engine turboprop") and maybe even trivial details like what we were having for breakfast. As the emotional impact had not yet occurred before these memories were formed, there must be a mechanism by which our brain retroactively incorporates these neutral details into a long-lasting emotional memory.

One mechanism may involve what has been referred to as "behavioral tagging." This mechanism proposes that experiences that are weakly encoded in the first place can be strongly *consolidated* if another more salient event occurs later. Behavioral tagging proposes that the weak and strong learning needs to rely on the same neural system (e.g., the hippocampus), that both events occur within a consolidation window of a few hours and that the strong event involves the release of dopamine (Moncada, Ballarini, & Viola, 2015). This mechanism has been revealed in rats by having rats learn an initial task at a weak level (only a few training trials) that would not normally generate a measurable long-term memory. If the weak training is hippocampal-dependent (e.g., context conditioning, object recognition, spatial learning) and followed up by a different but salient hippocampal-dependent experience (e.g., exploring a novel environment, as novelty exploration is naturally salient to rats and releases dopamine), then the weak training will be expressed *as if* it was strongly learned in the first place (Ballarini, Moncada, Martinez, Alen, & Viola, 2009; de Carvalho Myskiw, Benetti, & Izquierdo, 2013; Moncada et al., 2015). This behavioral effect is supported by a neural model of long-term memory known as synaptic tag-and-capture (Frey & Morris, 1997), which shows that a weak tetanus at a synapse generates a target ("tag") that can support persistent long-term potentiation if another, stronger potentiation occurs on another synapse in the same neural ensemble.

Behavioral tagging has been extended to the domain of episodic memory in humans. Dunsmoor, Murty, Davachi, and Phelps (2015) first presented neutral pictures from two object categories (animals and tools), and then paired different pictures from one of the categories (e.g., new pictures of animals) with an electrical shock. The emotional associative learning from the second phase of the experiment enhanced 24-hour memory for the pictures directly associated with the shock, compared to objects from the unpaired category (e.g., tools). Consistent with behavioral tagging, this enhancement in memory extended retroactively such that 24-hour recognition memory was selectively enhanced for related objects from the same category encoded *before* the shock was administered. This retroactive effect was not observed at an immediate memory test, suggesting that the effect was consolidation dependent. Another study in elementary school children in Argentina also supports a behavioral tagging hypothesis (Ballarini, Martínez, Perez, Moncada, & Viola, 2013). Children exposed to a novel science experiment or music lesson showed better memory for a story they had learned before the science experiment, as compared to children exposed to a familiar lesson plan after learning the story. Collectively, these studies show that emotion can enhance episodic memory for preceding neutral events and this enhancement effect cannot be confounded by differences in attention at the time of encoding.

Diminishing Unwanted Emotional Episodic Memories

Modulating the Consolidation of an Emotional Episodic Memory

There is an understandable desire to diminish the long-lasting emotional impact of highly negative experiences. Many forms of therapy aim to reduce the impact of negative memories through a variety of techniques (Craske et al., 2017). Exposure therapy, for instance, can diminish fear and anxiety through repeated exposure to stimuli with negative associations in a safe setting. To persistently diminish the impact of an unwanted memory, however, one highly effective technique would be to intervene in the formation of the memory in the first place. That is, to disrupt consolidation of an emotional memory.

In the laboratory study of learning and memory, postencoding manipulations can interfere with the formation of many types of memory (McGaugh, 2015; Wixted, 2004). For example, the acquisition of motor memory, skill learning, and word learning are all sensitive to retroactive interference from competing experiences soon after being formed. Hippocampal-based memories can also be diminished by targeting neurohormone systems associated with memory formation. These findings would suggest an ability to target the emotional enhancement of episodic memory by interfering with memory formation in the immediate aftermath of a highly negative experience.

In humans, the beta-adrenergic antagonist propranolol has been used to selectively diminish emotional enhancement effects in episodic memory. In a seminal study, Cahill, Prins, Weber, and McGaugh (1994) administered either propranolol or placebo before subjects heard a story that contained neutral and emotional details. Under placebo, subjects had better memory for the emotional details, as expected. Subjects on propranolol, however, showed weaker memory for the emotional details at a level equivalent to memory for the neutral details from the story. Notably, the drug was administered before subjects heard the story for peak plasma concentration to coincide with post-encoding consolidation period.

The idea of blunting the impact of arousal on the formation of unwanted emotional memories has implications for the treatment of PTSD. That is, if physiological arousal is reduced via a beta-blocker immediately after a trauma, then the expected boost in long-term memory for that emotional event will presumably be blocked. There are practical challenges in selectively thwarting the consolidation of emotional memories, however. Foremost, it is still not clear what precisely constitutes a consolidation period in different human memory systems. In Cahill et al. (1994) for example, drug administration occurred before emotional encoding to target consolidation, since memory might otherwise undergo early

stages of consolidation if the drug is administered after the event has occurred. This might explain why administration of a beta-blocker soon after trauma shows only limited efficacy at preventing PTSD (Sharp, Thomas, Rosenberg, Rosenberg, & Meyer, 2010), despite early reports (Pitman et al., 2002; Vaiva et al., 2003).

Modulating the Retrieval of Emotional Episodic Memories

An alternative approach is to attenuate the retrieval of emotional episodic memories. Although stress-related hormones can increase learning and consolidation of emotional episodic memory (Roozendaal et al., 2009), stress hormones impair *retrieval* of those memories (de Quervain, Roozendaal, & McGaugh, 1998). Interestingly, an initial study indicates that the administration of the stress hormone cortisol reduces the involuntary retrieval of traumatic memories in PTSD patients and self-ratings of traumatic symptoms (Aerni et al., 2004). However, stress-hormones generally impair memory retrieval overall, whereas as a treatment adjunct for PTSD one would optimally target only unwanted intrusive memories. Interestingly, the administration of a beta-blocker can specifically abolish the emotion-enhanced retrieval of emotional words and this abolishment persists in the absence of medication (Kroes et al., 2010). Whether blocking noradrenergic responses to diminish retrieval of traumatic memories is an effective treatment, however, remains to be seen, as blocking retrieval would presumably leave the stored traumatic memory intact and leave open the risk that symptoms would return.

Modulating the Reconsolidation of Emotional Episodic Memory

Identifying the precise timing of memory consolidation is a challenge, limiting the opportunity to interfere with the initial formation of an emotional memory in humans. This is especially challenging for old memories or for psychiatric conditions other than PTSD that are not marked by a precipitating event. An alternative approach that is gaining increasing interest in the neuroscience and clinical community is to take advantage of the *re*consolidation of an emotional memory (Lane, Ryan, Nadel, & Greenberg, 2015). Reconsolidation refers to the reactivation of a previously consolidated memory, returning it to a labile state and requiring protein synthesis to be maintained. During this period of reconsolidation, a reactivated memory is sensitive to modification by new experiences and drugs that affect a host of neural processes, most especially drugs that affect protein synthesis.

Most of the reconsolidation research is by far conducted in laboratory animals during conditioned learning tasks. This research will be described in the following section. There have been several demonstrations of effects consistent with reconsolidation in human episodic memory. Yet, most studies conducted to date are qualified by several caveats and alternative interpretations that do not rely on a reconsolidation mechanism. For example, a reminder of a previously memorized list of words can renew flexibility of that memory leading to intrusions from a subsequently presented list of words (Hupbach, Gomez, Hardt, & Nadel, 2007). However, in these studies, it is unclear if the memory impairment stems from a disruption of reconsolidation or confusion at the time of retrieval. Making use of the emotion-induced retrograde amnesia effect (Strange et al., 2003), the presentation of an emotional event following reactivation can result in a time-dependent impairment of a neutral episodic memory (Strange et al., 2010). Yet this is disturbance of neutral episodic memory not emotional episodic memory. Several studies have shown that administration of a beta-blocker prior to memory reactivation can diminish emotional episodic memory 1 day later in the absence of drug (Kroes et al., 2010; Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012). However, as beta-blockers can affect retrieval and most likely new learning at the time of memory reactivation, it is doubtful that these reports reflect an impairment of reconsolidation and thus a diminishment of the original emotional episodic memory. To circumvent this problem, Kroes and colleagues (2014) showed that a reminder of a previously learned emotional story followed by electroconvulsive therapy leads to time-dependent disruption of the memory for the entire reactivated story (but not a nonreactivated story), consistent with an impairment of reconsolidation.

Despite a variety of caveats, there is now a decent amount of evidence suggesting that emotional episodic memories can undergo reconsolidation. This provides a potential window of opportunity to modify unwanted memories. However, the translation of laboratory research on reconsolidation to clinical treatments has been limited. The contribution of emotional episodic memory to psychopathology is most pronounced in PTSD. People with PTSD experience involuntary intrusions of traumatic memories of severely distressing events. An initial open-label, not placebo-controlled clinical study targeting reconsolidation of traumatic memories with a beta-blocker found a reduction of hyperarousal responses in people with PTSD (Brunet et al., 2008), yet follow-up studies failed to replicate this effect (Wood et al., 2015). Furthermore, none of these studies found a reduction in intrusive trauma memories or clinical symptom scores in people with PTSD. A problem is that it is still unclear how to reactivate emotional episodic memories and what interventions are most effective in modifying reconsolidation of emotional episodic memories. Interestingly, the reduction in hyperarousal responses that Brunet et al. (2008) observed may

reflect an impairment of reconsolidation of emotional conditioned memories, which may be more sensitive to reconsolidation interventions. Next we will discuss emotional conditioned memories, a field that has largely developed independently from the study of emotional episodic memory.

Conditioned Fear Memories

Much of the research on basic mechanisms of learning and memory occurs in laboratory animals and involves relatively simple associative learning. In Pavlovian fear conditioning, for instance, the subject learns that a neutral sensory cue (CS, such as a tone or light) predicts an aversive event (US, such as an electrical shock). Learning to associate the CS with the US leads to a long-term memory of threat, such that the animal will display a conditioned defensive response (e.g., freezing) in the presence of the cue alone. This memory is formed after only one or a few learning trials and can persist for the lifetime of the animal. Note that the CS is initially neutral and only comes to evoke defensive responses by a remembered association with an aversive outcome. Fear conditioning has proved a foundational technique in behavioral neuroscience. Importantly, because the learning is salient and involves a high degree of arousal, findings from this research can be extended to understand *emotional* memory per se.

Here, we focus on fear conditioning as much of the progress on understanding emotional learning has been made using this technique. Notably, there is a large amount of animal learning that involves rewarding, rather than aversive, outcomes. This line of research is highly relevant to understand disorders like addiction and depression (Robinson & Berridge, 2008). Importantly, many of the findings on modifying appetitive or aversive memories indicate shared underlying processes, including the reconsolidation of old memories.

The Neurobiology of Fear Learning and Memory

Decades of research on the neurobiology of fear conditioning has detailed the critical role for the amygdala on the learning, consolidation, and storage of threat associations. Although a detailed review of this neurobiology is beyond the scope of this chapter (see Pape & Paré, 2010, for a comprehensive overview), the basic neurocircuitry involves sensory information reaching the basolateral amygdala via cortical and thalamic (subcortical) pathways and converging with sensory information concerning the aversive outcome. A number of other regions contribute to fear learning through feedback projections with the amygdala. This includes midbrain regions involved in learning from an unexpected shock

(prediction errors; McNally, Johansen, & Blair, 2011) and the hippocampus for contextual modulation of threat learning (Maren, Phan, & Liberzon, 2013).

This neurocircuitry has been extended to humans in the past 20 years using fMRI. A meta-analysis of fMRI studies of human fear conditioning shows activity to a CS associated with shock (vs. a within-subjects control stimulus never paired with shock) in the striatum, insula, dorsal anterior cingulate cortex, thalamus, and midbrain (Fullana et al., 2015). Interestingly, although early lesion studies supported a role for the human amygdala in fear conditioning (Bechara et al., 1995; LaBar, LeDoux, Spencer, & Phelps, 1995), activity in the amygdala is not consistently observed in human fMRI. The reasons for this could be due to issues inherent to imaging the amygdala, as it resides in a deep part of the brain susceptible to MRI artifacts. Another possibility is that the amygdala plays a unique role in the early phases of fear learning, and might be less critical once a subject learns the CS–US contingencies. But because most fMRI designs average activity over several trials, it may obscure the time-limited role of the amygdala in early learning. Indeed, some studies have reported early amygdala activity that habituates over time (Cheng, Richards, & Helmstetter, 2007). Alternatively, differential involvement of subregions or sparse representations may occlude observation of amygdala involvement in fear conditioning due to the spatial sensitivity of most fMRI methods (Bach, Weiskopf, & Dolan, 2011).

The Neurobiology of Fear Extinction

One of the earliest findings from classical conditioning research from Pavlov's laboratory was that repeatedly presenting the CS in the absence of the US resulted in a decrease in the conditioned response (Pavlov, 1927). This effect, referred to as extinction, was the topic of a number of studies throughout the early 20th century. Research on the topic never completely waned but, broadly speaking, the field of associative learning grew more interested in factors that affected the acquisition of conditioned learning rather than its extinction. With renewed interest in the neurobiology of fear conditioning in the 1990s, however, interest once again turned to extinction with the question of how the brain learns to extinguish conditioned fear and whether extinction memories are stored separately from conditioned fear memories.

Extinction is a particularly interesting phenomenon because it appears at first glance as if the animal has forgotten the association it had previously learned. That is, a rat who consistently and rapidly froze to a tone paired with shock freezes less and less during extinction to the point where it behaves as if the tone is unimportant. But if the experimenter waits some amount of time after extinction

and presents the tone again, the rat freezes as if it now expects the shock again. This postextinction recovery of the original behavior is highly reproducible and indicates that the animal did not forget the CS–US association. Extinction is instead viewed as a form of new learning that involves a secondary association between the CS and the *absence* of the US. The animal now has two conflicting associations with the CS (danger and safety) and thus two competing memories (Bouton, 2002). The memory of danger is highly generalizable (e.g., the CS can elicit defensive behavior when encountered in different places), whereas the memory of extinction is context specific (e.g., the CS is considered safe only in the place where it was presented without the shock). Therefore, the danger association is more likely to be reactivated under a variety of circumstances (but for a special case of extinction as unlearning, see Kim & Richardson, 2010).

Neurobiological research for laboratory animals has revealed neurocircuitry critical for fear extinction that includes the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus. Amygdala activation is required for the acquisition of extinction (Falls, Miserendino, & Davis, 1992), but the vmPFC (infralimbic cortex in rats) is involved in the consolidation and expression of extinction (Milad & Quirk, 2012) possibly via interaction with the hippocampus (Jin & Maren, 2015). Projections between the vmPFC and intercalated cells in the amygdala appear to inhibit the central nucleus of the amygdala preventing the expression of conditioned defensive responses (Tovote, Fadok, & Lüthi, 2015).

Neuroimaging research in humans affirms a role for the amygdala, vmPFC, and hippocampus in extinction learning. Amygdala activation is detected during extinction learning (Gottfried & Dolan, 2004; Knight, Smith, Cheng, Stein, & Helmstetter, 2004; Phelps, Delgado, Nearing, & LeDoux, 2004), and vmPFC activation is detected during both extinction learning and extinction retrieval (Kalisch et al., 2006; Milad et al., 2007; Phelps et al., 2004). In addition, hippocampal activation is detected during the retrieval of extinction in the extinction "context" (often a background image on which the CS is superimposed; Kroes et al., 2016; Milad et al., 2007). These neuroimaging findings support the concept that extinction is new learning that involves active processes in the brain to form an inhibitory "safety" memory.

Optimizing Extinction and Persistently Disrupting Conditioned Fear Memories

Extinction provides the empirical basis for psychotherapy that involves confronting feared stimuli or situations (i.e., exposure therapy). Exposure therapy is highly effective for a number of mental health disorders, including PTSD, specific phobias, obsessive-compulsive disorder, and social phobias. It is

not a coincidence that most of the disorders for which exposure therapy is most successful are those for which the etiology and maintenance of the disorder is well described by conditioning-based models (Bouton, Mineka, & Barlow, 2001; Mineka & Zinbarg, 2006). But despite a high rate of success, treated fear and anxiety can often return over time (Craske et al., 2017). Failures of exposure therapy to permanently attenuate fear and anxiety can be explained by the overall fragility of extinction as a form of secondary learning that has to compete against fear associations. Thus, there is a motivation to develop optimized fear extinction strategies in the laboratory that can be translated to achieve better clinical treatments.

One approach is to promote stronger and longer lasting extinction learning through pharmacological adjuncts that may act as cognitive enhancers. In laboratory animals the acquisition of extinction memory depends on glutamatergic *N*-methyl-d-aspartate (NMDA) receptors (Baker & Azorlosa, 1996). Stimulating NMDA receptors during extinction learning with D-cycloserine can improve extinction learning in rats (Walker, Ressler, Lu, & Davis, 2002) and exposure therapy in humans (Ressler et al., 2004). However, more recent studies and meta-analyses reveal only small positive effects of D-cycloserine on exposure treatment (Mataix-Cols et al., 2017; Otto et al., 2016). One reason for limited efficacy may be that if an exposure treatment session is unsuccessful, then D-cycloserine counterproductively strengthens fear associations (Mataix-Cols et al., 2017). That is, cognitive enhancers likely affect whatever learning is dominant at the time, be it safety learning or fear learning. Thus, clinicians should be attentive to the state of the patient before and during supervised pharmacotherapy with cognitive enhancers like D-cycloserine.

Another approach is to promote stronger extinction by optimizing behavioral strategies. A number of innovative approaches have been developed and tested in humans and laboratory animals. Many of these ideas spring directly from influential associative learning models that consider the role of prediction errors (Rescorla & Wagner, 1972), the ability to learn something new about the CS known as "associability" (Pearce & Hall, 1980), and the role of physical and temporal contexts (Bouton, 2004). These strategies include massively increasing the number of extinction trials, switching contexts during extinction to overcome the contextual specificity of extinction learning, presenting some aversive outcomes or a nonextinguished cue in compound with an extinguished cue, and replacing aversive outcomes with novel nonaversive outcomes (see reviews by Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Dunsmoor, Niv, et al., 2015). The success of these strategies is often measured by whether the extinguished cue later elicits a weaker conditioned response relative to a standard extinction protocol. Fortunately, these augmented forms of extinction are clinically tractable and could be tailored to enhance exposure therapy

(Vervliet, Craske, & Hermans, 2013). For example, knowledge that laboratory fear extinction is contextually specific provides empirical support for conducting exposure therapy across a range of environments.

Targeting Consolidation

As described in the preceding section on episodic emotional memories, the clearest way to prevent intrusive unwanted memories is to disrupt consolidation soon after a memory is formed. Two routes have been explored in an attempt to disrupt consolidation in fear conditioning: immediate pharmacological intervention and immediate extinction. Blocking protein synthesis in the basolateral amygdala is effective in animal models (Schafe & LeDoux, 2000) but direct injections of protein synthesis inhibitors is so far an unrealistic solution for clinical purposes. Because fear memories are facilitated by norepinephrine activation on beta-adrenergic receptors in the basolateral amygdala (Roozendaal et al., 2009; Sears et al., 2013), beta-adrenergic antagonists, like propranolol, are a feasible alternative to prevent fear-memory formation. Administration of beta-blockers—either directly into the amygdala (Bush, Caparosa, Gekker, & LeDoux, 2010) or systemically (Díaz-Mataix et al., 2017)—immediately prior to fear conditioning does diminish acquisition and long-term expression of a threat memory in rats. However, administration of propranolol appears to be less effective in preventing cued fear expression in humans (Grillon, Cordova, Morgan, Charney, & Davis, 2004). And, in animals, propranolol injected into the basolateral amygdala immediately *after* fear conditioning does not prevent memory consolidation (Bush et al., 2010; Schiff et al., 2017). The inability of an immediate posttraining beta-blocker to attenuate long-term memory might explain reports of failures of propranolol at preventing PTSD when administered soon after a trauma (Sharp et al., 2010).

Another strategy to disrupt memory formation is to immediately present conflicting information that retroactively interferes with the nascent memory. This strategy is effective for many types of learning, such as list learning (Müller & Pilzecker, 1900) and motor skill learning (Brashers-Krug, Shadmehr, & Bizzi, 1996). In conditioning, extinction represents the clearest form of retroactive interference, and thus it is possible that immediate extinction trials after fear conditioning will interfere with long-term memory formation. However, despite an initial report that immediate extinction greatly diminished long-term fear expression (Myers, Ressler, & Davis, 2006), many other reports have found the opposite result (Maren & Chang, 2006). That is, there is an "immediate extinction deficit" (Maren, 2013) wherein spontaneous recovery is stronger for immediate as compared to delayed extinction (see also Rescorla, 2004).

A similar immediate extinction deficit has been reported in humans as well (Huff, Hernandez, Blanding, & LaBar, 2009). One explanation is that stress levels following fear conditioning interferes with the ability to learn, encode, and later retrieve extinction memories (Maren, 2013).

As a practical matter, it is difficult to intervene with the formation of an emotional memory. And laboratory research on fear conditioning supports the idea that a long-term conditioned fear memory will likely form despite immediate pharmacological (Schiff et al., 2017) or behavioral intervention (Maren & Chang, 2006). A more practical approach is to target conditioned memories after they have formed.

Targeting Retrieval

A number of studies with laboratory animals have indicated that beta-blockers can reduce the retrieval of conditioned responses (Fitzgerald, Giustino, Seemann, & Maren, 2015; Muravieva & Alberini, 2010). These studies indicate that injection of a beta-blocker in the prelimbic cortex can reduce the retrieval of conditioned place preference (Otis, Dashew, & Mueller, 2013) and can normalize fear conditioning-related single cell activity (Fitzgerald et al., 2015). In humans, the administration of a beta-blocker can also attenuate the retrieval of fear conditioned responses and this is correlated with a reduction in dorsomedial prefrontal activity (Kroes et al., 2016). Thus, pharmacological approaches may reduce the retrieval of conditioned memories, but this does not modify the original memory itself, leaving open the possibility that fear responses will return.

Targeting Reconsolidation

Targeting memory reconsolidation is an optimal route to persistently alter or diminish the emotional impact of an old emotional memory (Lane et al., 2015). A landmark study in rats showed that re-presenting a CS opens the possibility to greatly diminish expression of a threat memory (Nader, Schafe, and Le Doux, 2000). In this study, a tone CS was paired with a shock US to form a conditioned memory in rats. Either 1 or 14 days later (to allow the memory ample time to consolidate), the tone was re-presented and a protein synthesis inhibitor was injected into the basolateral amygdala. This technique effectively eliminated the subsequent expression of the threat memory when tested the following day, and fear responses did not recover when tested at later time points. If memory was tested immediately after the reminder cue and administration of the protein

synthesis inhibitor, then rats did exhibit conditioned responses, indicating that the memory impairment was time-dependent. Furthermore, a fear-conditioned group that had protein synthesis administered without a reminder trial retained the threat memory, proving that memory reactivation was a key aspect to the design. This study indicates that a reminder cue can reactivate a conditioned memory and temporarily return it to a labile state requiring subsequent stabilization processes to be maintained. This finding has been replicated across a variety of amygdala-dependent tasks and species.

An intriguing ongoing debate is whether all types of threat memories retain the ability to undergo reconsolidation. A number of studies have indicated that older threat memories are insensitive to reconsolidation protocols (Frankland et al., 2006; Inda, Muravieva, & Alberini, 2011; Suzuki et al., 2004). This has led to the suggestion that reconsolidation may reflect a lingering phase of consolidation (Dudai & Eisenberg, 2004) and has obvious implications for reconsolidation-based treatment of old traumatic memories (Alberini, 2011). Interestingly, these studies have generally used tasks that initially depend on amygdala-hippocampus interactions (e.g., context conditioning, inhibitory avoidance learning), but then become independent from the amygdala and hippocampus (Frankland & Bontempi, 2005). This is in contrast to cue-conditioned memories that remain amygdala dependent (LeDoux, 2000). The sensitivity of reconsolidation interventions may thus differ between different types of memories and may be determined by systems-consolidation that results in distributed representations for some memories but not others (Kroes, Schiller, LeDoux, & Phelps, 2015). Yet other researchers reported that old fear conditioned memories, including initially hippocampal-dependent memories that have undergone systems-consolidation, can be disrupted by reconsolidation interventions (Debiec, LeDoux, & Nader, 2002; Einarsson & Nader, 2012; Gräff et al., 2014; Stern, Gazarini, Vanvossen, Hames, & Bertoglio, 2014; Taherian et al., 2014). Collectively these studies indicate that the question of whether all types of threat memories undergo reconsolidation is far from resolved and that it will likely depend on a complex interaction between the age of the memory, its dependence on different brain structures, the reactivation conditions and intervention methods.

In humans, the administration of a beta-blocker before or after memory reactivation can prevent the return of conditioned startle responses but leave expectancy ratings—a type of episodic memory—intact (Kindt, Soeter, & Vervliet, 2009; also see Chapter 2 of this volume). However, these results are not always replicated (Bos, Beckers, & Kindt, 2014). In a recent proof-of-concept study, volunteers with a strong fear of spiders were administered a beta-blocker and exposed to a live tarantula to activate their fear (Soeter & Kindt, 2015). Two weeks later, the participants were able to approach and interact with a tarantula

at a higher rate and for a longer period of time than participants who received the drug without activating their fear of spiders. This effect persisted for a year. Interestingly, the experimental group still expressed a subjective fear of spiders soon after treatment, but once they interacted with the spider, their subjective level of fear diminished. This implies that changing conditioned responses by targeting reconsolidation first allows for a change in behavior, which can then evoke a change in cognition. This promising proof-of-concept study will still require a full randomized controlled trial to establish whether research on reconsolidation of emotional conditioned memories can translate to an effective clinical treatment for phobias.

A nonpharmacological reconsolidation updating strategy developed by Monfils, Cowansage, Klann, and LeDoux (2009) involves presenting a single isolated trial ~10 minutes prior to a full extinction session. The isolated reminder trial consists of a previously fear conditioned stimulus, which presumably reactivates the fear memory. Memory reactivation thus provides an opportunity to persistently alter the memory trace during a reconsolidation time window by presenting the CS multiple times without the US. This procedure prevented return of freezing responses in rats across a variety of test conditions. The reminder + extinction procedure has also been reported to prevent the return of conditioned defensive responses in humans (Agren et al., 2012; Schiller et al., 2010; Steinfurth et al., 2014), but not all replications have been successful (Golkar, Bellander, Olsson, & Ohman, 2012; Soeter & Kindt, 2011). So how might the reminder + extinction procedure work? Reconsolidation and extinction appear to be mutually inhibitory processes (Merlo, Milton, Goozée, Theobald, & Everitt, 2014), such that the first presentation of a CS will reactivate the memory and trigger reconsolidation processes, but if it is rapidly followed by additional CS presentations, it initiates extinction processes that inhibit reconsolidation. The idea behind the reminder + extinction procedure is that if the isolated reminder CS is spaced far enough in time from the extinction CSs, the reconsolidation processes will have been triggered beyond a point where they can be inhibited by subsequent extinction CSs and, in turn, inhibit the initiation of extinction processes. Put differently, because the conditioned fear memory is first reactivated and in a labile state, extinction training will not form a separate safety memory but will instead overwrite the original fear memory during reconsolidation. In line with this idea, the reminder + extinction protocol reversed a neural signature (phosphorylation of GluR1) of the conditioned memory trace within the amygdala. The results of two neuroimaging studies suggest that the reminder + extinction procedure might modify the neural memory trace within the amygdala by preventing an inhibitory extinction memory trace from forming in the vmPFC (Agren et al., 2012; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Xue et al., 2012).

Another recent behavioral study in humans (Kroes, Dunsmoor, Lin, Evans, & Phelps, 2017) examined whether the reminder + extinction paradigm affected generalized responses to a broad conceptual category of fear conditioned objects. Subjects were first fear-conditioned using different exemplars from one of two animal categories (fish or birds). On the next day, one group received an isolated reminder trial from the feared category 10 minutes before the start of extinction. On the third day, subjects were tested for autonomic arousal (skin conductance responses) to novel images from the extinguished category. The reminder + extinction technique did not affect recovery of skin conductance responses to novel exemplars from the feared category the following day, as compared to a group who underwent standard extinction without a reminder trial. Interestingly, the reminder + extinction technique did affect *episodic* memory for fear conditioned exemplars. Subjects in the reminder + extinction group selectively recognized *more* items from the fear conditioned category than the control category as compared to subjects in the standard extinction group. Generalized memories that engage the episodic memory system may thus not be equally sensitive to reconsolidation intervention as simple sensory conditioned memories (e.g., geometric shapes). This may also explain why clinical translations have been more effective in reducing emotional conditioned memories that may underlie phobias and hyperarousal responses in PTSD but less effective in reducing more complex emotional episodic memories that contribute to intrusive trauma memories in PTSD. Furthermore, this study highlights that reconsolidation is a process of updating memories generally, meaning that reconsolidation can operate by either diminishing or enhancing consolidated memories. This is important to bear in mind when considering memory reconsolidation as a target for psychotherapy (Lane et al., 2015).

In sum, reactivated threat-conditioned memories can undergo a reconsolidation process during which they can be modified. This raises a potential opportunity to persistently modify unwanted memories and maladaptive behaviors during psychotherapy. However, the complexity, strength, and age of a memory limits the utility of current laboratory-based reconsolidation protocols, and may limit their effectiveness if directly translated to the clinic.

Conclusions

Here we have provided an overview of key historical and emerging trends in the neuroscience of emotional memory research. We discussed research on emotional episodic memory and conditioned learning, two forms of memory that have largely developed as separated academic fields. Contemporary investigations are revealing critical interactions between episodic and conditioned memory

systems. Understanding these interactions can provide unique insights into how emotion affects learning and memory, and vice versa. Ultimately, advances in the psychology and neuroscience of emotional memory will lead to a better understanding and innovative treatments for mental health disorders.

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