Cognitive neuroscience of emotional memory

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Abstract | Emotional events often attain a privileged status in memory. Cognitive neuroscientists have begun to elucidate the psychological and neural mechanisms underlying emotional retention advantages in the human brain. The amygdala is a brain structure that directly mediates aspects of emotional learning and facilitates memory operations in other regions, including the hippocampus and prefrontal cortex. Emotion–memory interactions occur at various stages of information processing, from the initial encoding and consolidation of memory traces to their long-term retrieval. Recent advances are revealing new insights into the reactivation of latent emotional associations and the recollection of personal episodes from the remote past.

Arousal
A dimension of emotion that varies from calm to excitement.

Valence
A dimension of emotion that varies from unpleasant (negative) to pleasant (positive), with neutral often considered an intermediate value.

Declarative memory
(Or explicit memory). Conscious memories for events and facts that depend on the integrity of the MTL.

Non-declarative memory
(Or implicit memory). Various non-conscious memories that are independent of MTL function and are expressed as a facilitation in behavioural performance due to previous exposure.

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Emotional memories constitute the core of our personal history. Philosophers and psychologists have long theorized about how emotion enhances or disrupts memory. Francis Bacon called strong emotion one of the six "lesser forms of aids to the memory"[1] and, more recently, Daniel Schacter referred to emotional persistence as one of the seven "sins of memory"[2]. Over the past century, emotional faculties were analysed primarily through the methods of animal behaviourism and social/clinical psychology, while being eschewed by traditional cognitive psychology. Cognitive neuroscientists have now reversed course to investigate how emotional events are learned and remembered in the human brain. These studies are beginning to elucidate the organization of emotional memory networks at the systems level, providing an important translational bridge between animal models and clinical disorders.

Emotion theorists often assume that affective space is parsed according to two orthogonal dimensions — arousal and valence. The impact of these dimensions on different forms of memory, including declarative (explicit) and non-declarative (implicit) memory, has been investigated. The current state of knowledge regarding emotional effects on these memory systems in humans is reviewed below, with an emphasis on arousal-mediated influences of the amygdala and its interactions with brain structures in the frontal and temporal lobes[3–5] (FIG. 1). The review encompasses several methods of cognitive and affective neuroscience, including studies of patients with medial temporal lobe (MTL) damage, neurohormonal manipulations and functional brain imaging. Within declarative memory, we focus mainly on memory for events, or episodic memory, and, in the case of non-declarative memory, we focus primarily on fear conditioning, as the greatest advances so far have been made in these areas. Most studies have examined emotional influences under conditions of moderately high arousal, but some studies on the effects of valence in the absence of high arousal are mentioned briefly. Although emotion predominantly benefits memory, long-lasting detrimental consequences are sometimes observed, particularly after severe or prolonged stress (BOX 1). Experimental support for classic views of emotional memory derived from research in non-human animals is described, in addition to findings that expand on this foundation to encompass domains of uniquely human aspects of recollection.

Emotional episodic memory

Consequences of amygdala damage. As in other domains of cognitive neuroscience, studies of brain-lesioned patients provide a core foundation to delineate structure–function relationships — in this case, determining which aspects of emotional memory depend on the integrity of the amygdala. In humans, organic syndromes rarely affect the amygdala selectively. If the brain damage extends to adjacent MTL memory structures bilaterally, the patient is rendered amnesic, which complicates the study of emotional effects. Therefore, key insights have been provided by post-surgical studies of temporal lobectomy patients with unilateral damage to the MTL due to epilepsy, as well as case studies of rare patients with selective bilateral amygdala pathology due to Urbach–Wiethe syndrome.

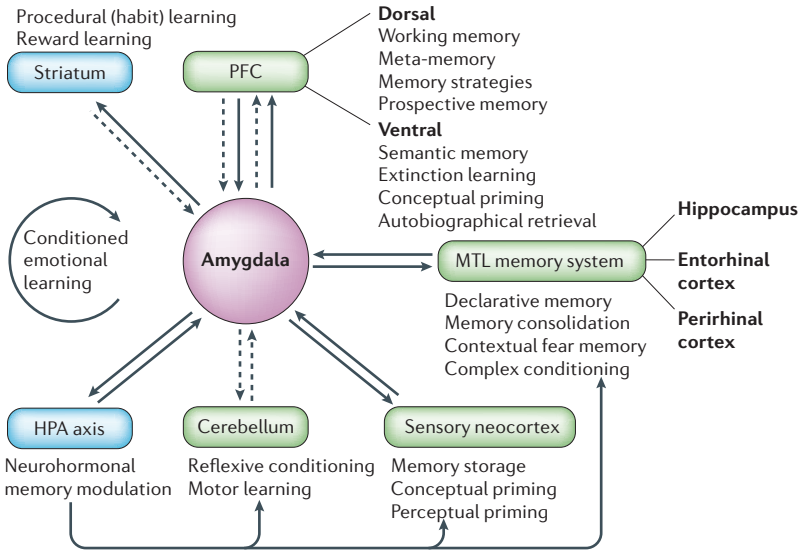

Figure 1 | **Potential mechanisms by which the amygdala mediates the influence of emotional arousal on memory.** In addition to emotional learning that takes place intrinsically in the amygdala, direct and indirect neural projections target several memory systems in the brain, including those that subserve working memory, declarative memory and various non-declarative forms of memory (for example, procedural learning, priming and reflexive conditioning). Complex conditioning refers to various higher-order conditioning procedures that are hippocampal dependent, including trace conditioning and conditional discrimination learning. The amygdala also triggers the release of stress hormones by way of the hypothalamic–pituitary–adrenal (HPA) axis, which feed back onto memory consolidation and storage sites as well as the amygdala itself to enhance memory over longer time intervals. Solid arrows indicate direct connections, dashed arrows indicate indirect connections. Blue labels indicate connections with subcortical structures. MTL, medial temporal lobe; PFC, prefrontal cortex.

Since the seminal findings of Kleinsmith and Kaplan[6], behavioural studies in healthy adults have shown that emotional advantages in memory are sometimes augmented over time. For example, retention advantages for emotionally arousing words relative to neutral words are greater when memory is tested after long (1 h to 1 day) than after short (immediate) delay intervals[7,8]. Such observations provide evidence that emotional arousal benefits memory in part by facilitating consolidation processes, which take time to emerge. Temporal lobectomy patients do not show enhanced arousal-mediated memory consolidation but instead show parallel forgetting rates for arousing and neutral words from immediate to 1-h retention intervals[7,9]. However, the exact time course of consolidation is subject to considerable debate, and stabilization of memory traces is a protracted process that could last from months to years. Urbach–Wiethe syndrome patients also show impairments in long-term (1 h to 1 month) recall or recognition of emotional words, pictures and stories[10–12] (FIG. 2). Although these results have also been interpreted to reflect deficits in emotion-enhanced consolidation processes, we note that short-term memory for these items has not been tested.

Emotional arousal has complementary, immediate effects during encoding that are time invariant and are interpreted to reflect attentional influences on memory[3]. One additional consequence of emotional arousal is the focusing of attention on central gist information at the expense of peripheral details for complex events such as emotional narratives or social encounters, as exemplified by 'weapon focus' in eyewitness testimony research. Attentional focusing ensures that emotionally salient features of complex events are preferentially retained in memory, which confers evolutionary advantages. Patients with amygdala lesions do not focus on central gist information when memory is tested for audiovisual narratives that describe emotionally arousing events[13]. The gist memory effects are evident when the patients generate intact skin conductance responses (SCRs) and arousal/valence ratings to the stimuli, which implicates impairments in emotion–cognition interactions rather than a more basic problem with emotional evaluation.

In contrast to the above findings, certain aspects of emotional memory are preserved following amygdala damage. Patients with amygdala lesions do preferentially remember words that are affectively valent but low in arousal relative to neutral ones, as well as neutral words encoded in emotional sentence contexts relative to neutral contexts[9,14]. In such cases, it is possible that the patients access other cognitive resources that boost retention, including semantic cohesion[15] and organizational strategies, which are probably mediated by direct interactions between the MTL and the prefrontal cortex (PFC). Some emotional benefits in memory are therefore possible without a fully functioning amygdala, especially when damage occurs later in life[16], and relate in part to recruitment of cognitive processes by emotional valence. These findings extend the results from research in rodents to suggest that arousal rather than valence is the crucial factor in engaging the amygdala during emotional memory tasks[17].

Neurohormonal memory modulation. A limitation of most patient studies is that impaired performance observed at a single time point could reflect deficits in any one of four memory stages: encoding, consolidation, storage or retrieval. Psychopharmacological studies in healthy adults can provide somewhat greater specificity regarding which phase of memory is affected by emotion. However, the prolonged time course of neurohormonal actions must be considered, as stress hormones can have different effects on each stage of memory.

As shown in rodents by McGaugh and colleagues[18,19], adrenal stress hormones modulate performance on various learning and memory tasks. Emotional situations initiate complex interactions between adrenergic and glucocorticoid systems that are coordinated by the hypothalamic–pituitary–adrenal axis at central and peripheral sites of action. Adrenaline release in the periphery stimulates vagal afferents that terminate in the nucleus of the solitary tract, which, in turn, projects to the amygdala and other memory-related forebrain regions. Post-training infusion of β-adrenergic receptor antagonists into the basolateral amygdala blocks the memory-enhancing effects of adrenaline, and infusion of β-adrenergic receptor agonists facilitates memory consolidation[20,21]. Within the basolateral amygdala and hippocampus, noradrenaline enhances glutamatergic synaptic plasticity, which is thought to underlie learning and memory functions[22,23].

Recollection
Episodic retrieval that is accompanied by recovery of specific contextual details about a past event.

Urbach–Wiethe syndrome
(Or lipoid proteinosis). A rare, hereditary, congenital disorder characterized by systemic deposits of hyaline material that are prominent in the skin, oral mucosa and pharynx. About 50% of all cases have additional intracranial deposits in the MTL, which occasionally target the amygdala selectively.

Box 1 | **Post-traumatic stress disorder**

Post-traumatic stress disorder (PTSD) emerges after exposure to a traumatic stressor that elicits fear, horror or helplessness and involves bodily injury or threat of injury or death to one's self or another person. Community-based studies in the United States estimate a lifetime prevalence of trauma exposure at 50%, but only 5% of men and 10% of women will develop PTSD[139]. Prevalence rates are higher in at-risk populations, such as war veterans. Diagnostic symptoms include persistent re-experiencing of the traumatic event, avoidance of reminders, numbing of responsiveness and heightened arousal. Neurobiological models of PTSD have focused on brain regions and stress hormone systems that are involved in fear, arousal and emotional memory. Cortisol dysregulation and abnormal responses to adrenergic modulators implicate disturbances in the hypothalamic–pituitary–adrenal axis and its interactions with brain regions that control arousal[140]. Chronic stress in PTSD contributes to smaller hippocampal volume and declarative memory deficits[141]. Symptom provocation studies show blood flow changes in cortico-limbic circuitry involved in emotional memory, including the amygdala, anterior cingulate and orbitofrontal cortex[142,143]. Patients with PTSD have exaggerated startle responses to loud sounds[144] and show greater contextual and cued fear conditioning[145,146]. Given that administration of the β-adrenergic receptor antagonist propranolol selectively reduces memory consolidation for emotionally arousing material (FIG. 2), beta-blockers are currently being evaluated as potential agents for secondary prevention of PTSD[147]. However, the ethics of this approach, as well as its empirical and theoretical basis, is still the subject of some debate.

Memory consolidation for both appetitively and aversively motivated learning tasks is blocked by adrenocortical suppression, and is enhanced by infusions of glucocorticoid receptor agonists into the basolateral amygdala and hippocampus[24–26]. Lesions of the basolateral amygdala modulate the effectiveness of glucocorticoid manipulations in the hippocampus, which implicates a functional coupling between these regions for arousal-enhanced memory consolidation[25]. Because the behavioural impact of stress and glucocorticoids is modulated by α- and β-adrenergic receptor activation in the basolateral amygdala, the mnemonic effects of different stress hormone systems are co-dependent[27,28]. Collectively, the findings from research in rodents have been interpreted as evidence to support the memory-modulation hypothesis, which states that greater long-term memory for emotional than neutral events reflects the neuromodulatory influence of the amygdala on consolidation processes in MTL memory regions through engagement of stress hormones[18]. Analogous neurohormonal mechanisms also contribute to amygdala influences over other memory-processing regions of the brain, although the behavioural consequences are not always advantageous. For example, acute corticosterone administration impairs performance on tests of working memory, which also depend on adrenaline and on interactions between the amygdala and PFC[29].

Investigations with humans have begun to examine neurohormonal influences across emotional and non-emotional memory tasks. In patients with epilepsy, recognition memory for prose passages is enhanced following moderate-intensity stimulation of the vagus nerve, which provides a route for peripheral hormones to feed back onto central learning sites[30]. Pharmacological manipulations in humans have implicated both adrenergic and corticosteroid influences on memory, although with less anatomical specificity than in animal studies. Administration of β-adrenergic receptor antagonists (for example, propranolol) before encoding reduces the long-term retention advantage typically seen for emotionally arousing stimuli relative to neutral stimuli[31,32] (FIG. 2). Conversely, administration of β-adrenergic receptor agonists (for example, yohimbine) promotes emotional memory[33,34]. However, one study found that 40 mg of propranolol does not affect emotional memory when administered after encoding[35], and another study found impairing effects of a higher dose (80 mg) of propranolol across both short- and long-term retention intervals[36]. During short retention intervals, propranolol also induces a retrograde amnesia for neutral words that precede emotional words in a list, an effect that is larger in females[37]. Additional research in humans is warranted to dissociate adrenergic modulation of attentional effects during encoding (that affect both short- and long-term memory) from consolidation effects, which have been shown consistently in rodents.

Comparison of adrenergic receptor antagonists that readily cross the blood–brain barrier (for example, propranolol) versus those that do not (for example, nadolol) shows that β-adrenergic effects on emotional memory in humans are mediated by receptors located in the brain[32] (but see REF. 38 for an alternative point of view). Neuropsychological and functional neuroimaging studies have converged to identify the amygdala as a likely mediator of these influences. On tests of memory for emotionally arousing words or stories, damage to the amygdala yields impairments similar to those of beta-blocker administration in healthy controls[9,11,12,37,39] (FIG. 2). In addition, functional neuroimaging studies indicate that amygdala activity during the encoding of emotional stimuli is reduced by propranolol[40,41], with a concomitant reduction in hippocampal activity during retrieval of the same stimuli[40].

Stress and glucocorticoids affect both emotional and non-emotional forms of memory in humans. During encoding, acute cortisol administration or stress-induced endogenous cortisol release generally enhances emotional learning and memory[42–45], but similar manipulations during retrieval impair recall of earlier memories[46,47]. The acute impact of cortisol is typically greater for emotionally arousing stimuli than it is for neutral stimuli, although some studies have found similar effects across emotional and neutral material[48], or effects in the opposite direction[49,50]. On tests of working memory, psychosocial stress or high-dose cortisol administration typically impair performance, which is consistent with the animal literature[51–53].

Variations in cortisol influences on memory are attributable to several factors, including biological sex, duration of stress (acute versus chronic), cortisol dose (typically as an inverted U-shaped function) and time of day relative to the circadian flux in endogenous cortisol levels[18,19]. Variations caused by cortisol dose and time of day relative to circadian flux are related to the relative occupancy of mineralocorticoid or glucocorticoid receptor subtypes, which have different affinities for glucocorticoids and affect memory functions to different extents. At low doses, mineralocorticoid receptor activation is dominant and relates to emotional enhancement of encoding processes, but consolidation benefits are typically not reported. At higher doses, glucocorticoid receptor activation,

Working memory
A form of memory in which stimulus representations are actively maintained and/or manipulated in conscious awareness over a short period of time.

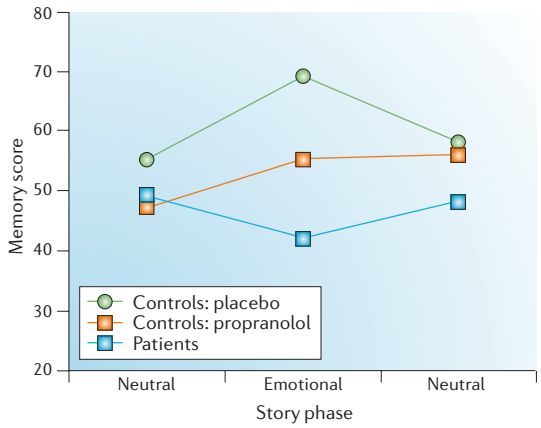

Figure 2 | **β-Adrenergic receptor blockade in healthy adults during encoding produces similar deficits to amygdala damage on a test of emotional memory.** Participants view a slide show and hear an accompanying narrative. The middle portion of the story describes a car accident, whereas the beginning and end portions of the story are emotionally neutral in content. Healthy adults given a placebo 1 h before the story remember the emotionally arousing portion of the story better than the neutral portions 1 week later. Propranolol administration during encoding abolishes this retention advantage in healthy adults. Two patients with selective amygdala damage (SM and BP, data averaged) also lack the retention advantage for the emotionally arousing portion of the story. Modified, with permission, from REF. 12 © (1997) Cold Spring Harbour Laboratory Press and REF. 31 © (1994) Macmillan Magazines Ltd.

combined with adrenergic influences, contributes to enhanced memory consolidation. In contrast to acute effects, chronic elevations in basal cortisol levels in older high-stress individuals[54] or altered stress reactivity in some neuropsychiatric disorders, such as depression[55] and post-traumatic stress disorder (BOX 1), can lead to reductions in hippocampal volume and concomitant declarative memory deficits, even for non-emotional material. Cortisol-induced impairments in declarative memory retrieval have been linked to reductions in MTL activity[56]. However, as mentioned above with respect to working memory, stress hormone systems project to a diffuse set of brain areas (including the PFC, cerebellum, hypothalamus and hippocampus), each of which are subject to modulation by the amygdala for different memory operations with potentially distinct consequences (FIG. 1).

Imaging emotional memory encoding. Brain imaging using positron emission tomography (PET) and functional MRI (fMRI) can also distinguish the impact of emotion at different stages of episodic memory, but with far superior specificity of the underlying neuroanatomy than hormonal manipulations. Moreover, these studies have the potential to reveal functional interactions among distributed brain regions to test the memory-modulation hypothesis and to implicate involvement of additional areas. Most functional imaging studies on this topic have investigated encoding processes[57–67]. Consistent with the memory-modulation hypothesis, activity in the amygdala and MTL memory regions during the encoding of emotional stimuli is correlated with individual differences in later memory for these stimuli. PET studies initially established that the amount of amygdala activation during encoding positively correlates with delayed recall accuracy for aversive but not neutral film clips[57], as well as delayed recognition accuracy for emotionally arousing pictures that are both positive and negative in valence[59]. In addition, there is a sex difference in the hemispheric distribution of encoding-related amygdala activity, with men showing right-lateralized effects and women showing left-lateralized effects[61]. The sexually dimorphic lateralization pattern is more prominent when considering the relationship between amygdala activity and memory, and is found less often as an effect of emotion on perceptual processing. Reasons for the sex difference in emotional memory remain unclear and constitute an active area of current research.

Event-related fMRI experiments have replicated the correlation between amygdala activity at encoding and delayed retention accuracy for emotional pictures, as well as the dependency of this relationship on self-reported arousal levels and lateralization by sex[60,62,63]. Confirmation by this technique is important because the temporal resolution of PET and fMRI when using blocked designs does not permit researchers to distinguish transient emotional effects from sustained mood influences, and individual items cannot be analysed according to emotion ratings or memory performance (for example, retrieval success or failure) obtained from each participant. Furthermore, event-related designs allow the use of the subsequent memory paradigm, which can distinguish activity associated with stimulus processing and task demands to reveal neural signatures that specifically reflect successful encoding operations. This paradigm isolates the Dm effect by contrasting study-phase activity for items that are remembered versus those that are forgotten in a subsequent memory test[68]. The enhancing influence of emotion on successful encoding activity can then be investigated by comparing the Dm effect for emotional versus neutral stimuli.

For example, an event-related potential (ERP) study showed that the Dm effect for emotional stimuli occurred faster (400–600 ms) than the Dm effect for neutral stimuli (600–800 ms), suggesting that emotional stimuli have privileged access to processing resources[69]. Consistent with the memory-modulation hypothesis, fMRI studies have shown that emotion enhances the Dm effect in both the amygdala and MTL memory regions[60,62,64,65,70] (FIG. 3). In addition, the Dm effect for emotional and neutral items differs in localization within the MTL, with the former being mediated in anterior parahippocampal regions and the latter in posterior parahippocampal regions[64]. This functional localization is consistent with anatomical evidence for greater reciprocity between the amygdala and anterior sectors of the parahippocampal gyrus[71,72]. Although MTL structures have been emphasized in support of the memory-modulation hypothesis, we note that the PFC also contributes to emotional Dm effects, with regionally specific modulation by both arousal and valence[65,67,73] (FIG. 3).

Dm effect
An index of brain activity at encoding that distinguishes subsequently remembered from subsequently forgotten items and is assumed to reflect successful encoding processes.

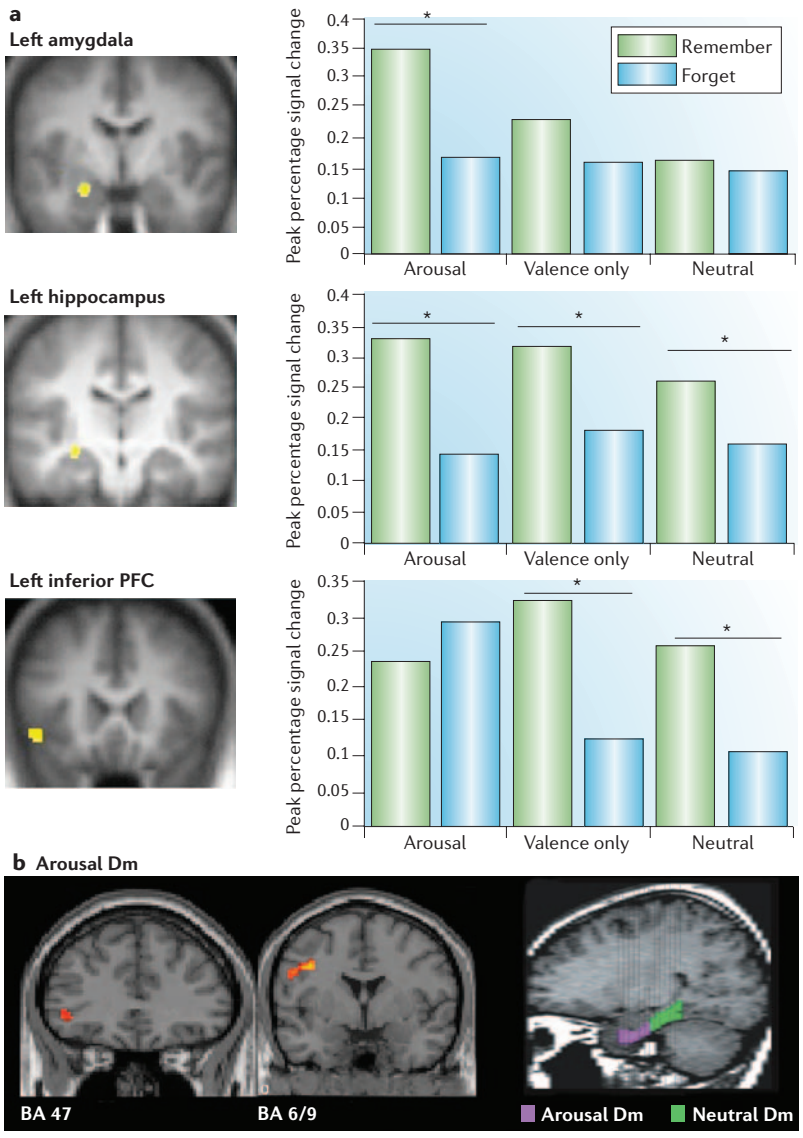

Figure 3 | **Two routes to emotional remembering: arousal- and valence-mediated subsequent memory effects. a** | Functional MRI (fMRI) activation is monitored while healthy adults encode high-arousing negative words, low-arousing negative words (valence only) and neutral words. For each participant, the data from each trial are sorted off-line according to whether the word is subsequently remembered or forgotten to generate an index of successful encoding (called the Dm effect or subsequent memory effect). Relative to neutral words, high-arousing negative words generate greater Dm effects in the hippocampus and amygdala, whereas low-arousing negative words generate greater Dm effects in the hippocampus and a posterior region of inferolateral prefrontal cortex (PFC). Asterisks indicate significant differences ($p < 0.05$) between fMRI activation for remembered versus forgotten items within each condition. **b** | Arousal-mediated Dm effects are elicited in other sectors of PFC and are distributed more anteriorly along the longitudinal axis of the parahippocampal gyrus than neutral Dm effects. BA, Brodmann's area. Panel **a** modified, with permission, from REF. 65 © (2004) National Academy of Sciences. Panel **b** reproduced, with permission, from REF. 64 © (2004) Cell Press and REF. 73 © (2004) Elsevier Science.

Familiarity
Episodic retrieval that is accompanied by a feeling that an event happened in the past, although no contextual details are available.

The memory-modulation hypothesis predicts not only greater activity in the amygdala and the MTL memory system during successful emotional encoding, but also greater interaction between these regions. Several lines of evidence support this prediction (FIG. 4). First, structural equation modelling of PET data shows greater amygdala–parahippocampal interactions during the encoding of negative compared with neutral film clips[58]. Second, in patients with epilepsy with varying degrees of MTL sclerosis, pathology severity in the left amygdala is inversely correlated with emotional encoding activity in the left hippocampus and is associated with a compensatory shift to the right hippocampus, whereas pathology severity in the left hippocampus generates an analogous effect in the amygdala[66]. Finally, in healthy participants, the Dm effects in the amygdala and in the entorhinal cortex are positively correlated during the encoding of emotionally arousing but not neutral pictures[64]. Similar emotion-specific Dm correlations are also found between the amygdala and the hippocampus[64,65].

Imaging emotional memory retrieval. Classic views of amygdala function have emphasized its role during the encoding and consolidation stages of memory rather than during retrieval[18]. Recent research in rodents suggests that the amygdala also contributes to the reconsolidation of emotional memory traces following their retrieval[74]. In humans, few neuroimaging experiments have targeted the retrieval stage of emotional episodic memory. Early studies implicated extrastriate cortex[75,76] as well as the anterior temporal lobe and amygdala[77] in aspects of emotional stimulus retrieval. Owing to the use of blocked designs, these studies suffered the same limitations as those described above for memory encoding. More recently, ERP and event-related fMRI paradigms were used to investigate the retrieval of neutral items that were encoded in emotional versus neutral contexts. ERP shifts in frontal, temporal and parietal sites distinguished retrieval of items encoded in emotional versus neutral contexts, and items successfully retrieved from emotional contexts elicited fMRI activation in limbic structures (amygdala, insula and cingulate) and various regions within temporal and frontal neocortex[78–81]. Contextual memory paradigms have experimental advantages in that they avoid the confounding influence of emotion on perception when emotional stimuli are used as retrieval cues, but they assess the retrieval of emotional context rather than emotional content, which might not rely on the same mechanisms[82].

One method for investigating the retrieval of emotional events while controlling for confounding perceptual influences is to identify successful retrieval activity by comparing responses to successful ('hits') versus unsuccessful ('misses') retrieval trials. Emotional enhancement of retrieval is then measured by subtracting successful retrieval activity for neutral items from that for emotional items. Furthermore, by using participants' responses in the scanner, it is possible to distinguish those emotional memories that are accompanied by a sense of recollection rather than familiarity. These two retrieval processes rely on different cognitive and neural mechanisms[83], and recollection is especially enhanced behaviourally by emotion[84,85]. Dolcos and colleagues[86] investigated the impact of emotional content on successful retrieval activity associated with recollection or familiarity. Participants were scanned 1 year after the original encoding to avoid

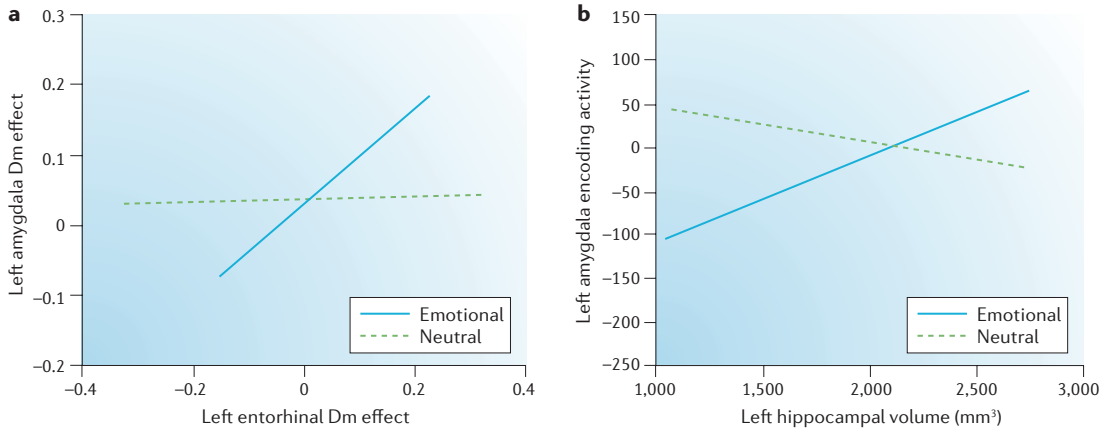

Figure 4 | **Interactions between the amygdala and medial temporal lobe memory system during encoding predict emotional retention advantages and recollection-based emotional retrieval. a** | Whereas arousal-based Dm effects in the amygdala and entorhinal cortex are correlated in individual participants, neutral Dm effects are not. Similar emotion–memory interactions occur between the amygdala and hippocampus (data not shown). The *x* and *y* axes plot regression lines for the correlation values. **b** | In patients with medial temporal lobe epilepsy, left hippocampal volume correlates with ipsilateral amygdala activity that distinguishes emotional words later retrieved with a sense of recollection ('remember' hits) from those later retrieved with a sense of mere familiarity ('know' hits). A compensatory activity shift to the contralateral amygdala is also observed, and structural integrity of the left amygdala has an analogous effect on functional MRI activity in the hippocampus (data not shown). The reciprocal co-dependence between the amygdala and hippocampus is greater during encoding of emotional relative to neutral words. The *y* axis represents response estimates for successful encoding activity in arbitrary units. Panel **a** modified, with permission, from REF. 64 © (2004) Cell Press. Panel **b** modified, with permission, from REF. 66 © (2004) Macmillan Magazines Ltd.

confounding emotional influences on retrieval with influences on consolidation, which is a potential problem in studies using short (<1 h) retention intervals. As depicted in FIG. 5, greater retrieval success activity was found in the amygdala, hippocampus and entorhinal cortex for emotional relative to neutral pictures. In the amygdala and hippocampus (but not the entorhinal cortex), this activity was enhanced for emotional items recognized with a sense of recollection rather than familiarity (see Sharot *et al.*[87] for another demonstration of recollection-specific emotional retrieval in the amygdala). Moreover, similar to findings from the encoding stage (FIG. 4), the correlation between successful retrieval activity in the amygdala and MTL memory regions was greater for emotional than for neutral stimuli. Therefore, the functional interactions between the amygdala and MTL memory system extend to successful retrieval of more remote emotional memories, particularly those retrieved with a sense of recollection, and are not limited to the encoding and consolidation stages of memory.

One year is perhaps a limiting retention interval to evaluate brain mechanisms of emotional retrieval using laboratory-based tasks owing to the time course of forgetting. However, retrieval of older emotional memories can be investigated in the domain of autobiographical memory. Studies of retrograde amnesia support Markowitsch's proposal[88] that retrieval of remote personal memories involves interactions between the inferior PFC and its connections with the anteromedial temporal lobe that course through the uncinate fasciculus[89,90]. Brain imaging of autobiographical retrieval in healthy adults confirms engagement of these frontotemporal regions, as well as others, including medial PFC, retrosplenial cortex, precuneus and extrastriate cortex, that link the memories to brain systems that support self-referential processing and visuospatial imagery[91–96]. Emotional intensity also affects the perceptual and phenomenological properties of autobiographical memories, such as the degree to which the memory is re-lived on retrieval, the vividness of the memory and narrative detail[85]. The neurobiology underlying these experiential influences is not well-characterized. Understanding how emotion transforms the recollective experience that accompanies autobiographical memories can advance knowledge about complex, subjective features of emotional memory in ways that go beyond traditional laboratory-based models.

Fear conditioning

Role of the amygdala. In the domain of non-declarative memory, Pavlovian conditioning has provided the most widely studied model of emotional learning, and the neural mechanisms are highly conserved across species. During fear conditioning, subjects rapidly acquire fear to a previously innocuous stimulus (the conditioned stimulus; CS) that predicts the occurrence of a noxious event (the unconditioned stimulus; US). Subsequent presentations of the CS in the absence of reinforcement extinguishes the conditioned associations and fear responses subside. In humans, fear conditioning is typically measured by monitoring skin conductance responses (SCRs) or the potentiation of eyeblink startle reflexes. Consistent with the biological preparedness theory, conditioning to fear-relevant stimuli, including snakes/spiders, fearful/angry facial expressions and faces of other social groups, is less resistant to extinction and can be acquired unconsciously using

Biological preparedness theory
A theory proposed by Martin Seligman that considers phobias as arising from a selective set of biological associations that the organism is evolutionarily tuned ('prepared') to learn, which leads to rapid fear acquisition and persistence of fear.

Visual masking
A psychophysical technique that can be used to reduce perceptual awareness of visual stimuli by presenting them briefly (for typically < 33 msec) on a computer screen or tachistoscope and immediately displaying another stimulus of equal or greater complexity ('backward' masking). Participants report seeing only the second stimulus, although the visual system processes aspects of the masked stimulus.

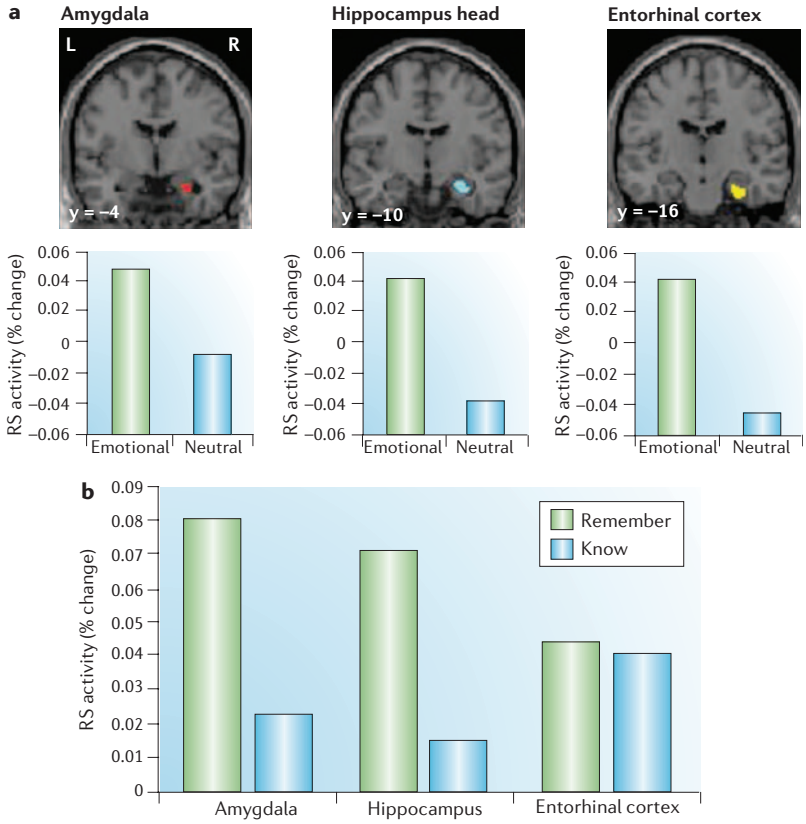

Figure 5 | **Successful retrieval of emotionally arousing memories from long-term storage depends on the amygdala and medial temporal lobe memory system. a** | Retrieval success (RS) measures the difference in activity in response to pictures that are successfully retrieved ('hits') from those that are unsuccessfully retrieved ('misses'). Functional MRI data are obtained from healthy adults during a recognition memory test conducted 1 year after encoding. The amygdala, hippocampus and entorhinal cortex show enhanced RS activity for pictures with emotionally arousing content relative to those with neutral content. **b** | The amygdala and hippocampus further differentiate emotional pictures that are successfully retrieved with an accompanying sense of recollection ('remember' hits) from those that simply seem familiar ('know' hits). Data in **a** and **b** represent the maximum percentage signal change taken from voxels in the shaded regions relative to the pre-stimulus baseline. Panels **a** and **b** modified, with permission, from REF. 86 © (2005) National Academy of Sciences.

visual masking techniques[97,98]. Subliminal fear conditioning has been influential in characterizing how fear and anxiety can arise in the absence of awareness on the part of the individual. Given the putative role of this form of emotional learning in traumatic memory formation, anxiety disorders (including phobias) and drug addiction, much effort has been made to understand the psychological and neural mechanisms of conditioned behaviour.

A rich tradition of neuroscientific research in rodents has elucidated the crucial role of the amygdala in conditioned fear learning. Lesions of the basolateral and central nuclei of the amygdala prevent the acquisition of fear to discrete cues and environmental contexts[99,100]. Neurons in the lateral amygdala integrate sensory information with nociceptive information and are proposed to form cell assemblies that mediate the formation of CS–US associations[101]. During fear conditioning, electrophysiological changes occur in the lateral amygdala before they do in other brain regions[102], and amygdala lesions reduce synaptic plasticity occurring in the thalamus and cortex[103,104]. Fear conditioning induces long-term potentiation, a form of synaptic plasticity that is thought to underlie learning, along both subcortical and cortical routes of information processing to the amygdala[105–107]. After the induction of long-term potentiation, activation of various intracellular processes within the amygdala leads to gene transcription and protein synthesis that generate cytoskeletal and adhesion remodelling, which stabilize functional alterations between synaptic contacts and preserve fear learning[108]. To extinguish fear behaviours, the ventromedial PFC suppresses amygdala function by engaging a network of inhibitory interneurons[109,110]. These observations in non-human animals position the amygdala centrally in an integrated network that underlies fear learning and its extinction.

In humans, damage to the amygdala consistently impairs fear conditioning and fear-potentiated startle responses, similar to those observed in non-human animals[9,111–116]. Because patients with amygdala lesions can verbalize the reinforcement contingency and can generate unconditioned SCRs to noxious stimuli, the findings implicate a deficit in an implicit emotional learning mechanism rather than one related to explicit memory or fear expression. By contrast, amnesic patients with damage restricted to the hippocampus show the opposite dissociation — they can acquire conditioned fear on simple tasks but cannot verbalize the appropriate stimulus relationships[111,117]. Together, these results constitute a double dissociation regarding the contributions of the amygdala and hippocampus to conditioned emotional learning in humans (FIG. 6). This distinction is important because, unlike rodents, humans acquire conscious knowledge of the stimulus relationships, which can modify learning under some circumstances[118]. The neuropsychological findings provide evidence that the declarative and non-declarative aspects of simple forms of fear learning are neurally dissociable.

Contextual reinstatement of fear. Although the initial acquisition of simple fear conditioning to sensory cues depends on the amygdala and not the hippocampus, other aspects of conditioning are hippocampal dependent, including the contextual reinstatement of extinguished fear. The suppression of conditioned fear that accompanies extinction training is highly sensitive to environmental manipulations, and extinguished fear responses can be renewed or reinstated over time, depending on the context in which the CS is presented. Bouton has theorized that reinforced (CS–US) associations from acquisition training and non-reinforced (CS but no US) associations from extinction training are overlaid in memory, and that contextual cues disambiguate which of these memories is dominant when a CS is encountered after extinction[119]. As a result, currently available contextual information guides the selection of an appropriate behavioural response to signals of threat following extinction training. Rodent lesion studies have shown that the integrity of the hippocampus is important for the contextual recovery of extinguished fear[120]. Behavioural

Renewal
After extinction training, conditioned fear can be renewed by presenting the conditioned stimulus in a novel context.

Reinstatement
After extinction training, conditioned fear can be reinstated by presenting the conditioned stimulus in a context in which a noxious or stressful stimulus was recently encountered.

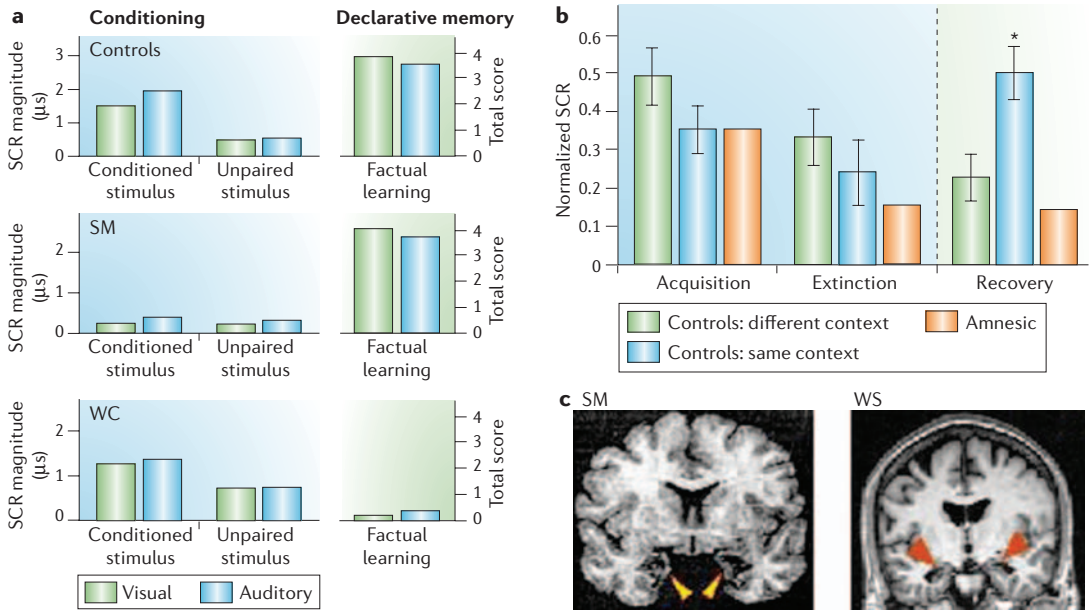

Figure 6 | **Studies of patients with rare brain lesions reveal dissociable contributions of the amygdala and hippocampus to conditioned fear learning. a** | A patient with selective amygdala damage (SM) has intact factual knowledge regarding the stimulus contingencies but fails to acquire skin conductance responses (SCR) to visual or auditory cues (conditioned stimuli) paired with a loud noise. A patient with amnesia due to selective hippocampal damage (WC) shows the opposite dissociation — an inability to acquire factual knowledge but intact conditioned fear responses. Healthy controls acquire both factual knowledge and conditioned fear to stimuli that predict reinforcement relative to unpaired control stimuli. **b** | The contextual reinstatement of extinguished fear is hippocampal dependent. Healthy participants acquire and extinguish SCRs to a visual stimulus that predicts shock delivery. After extinction, participants are given a few presentations of the shock alone either in the same testing context or a different testing context (at time point indicated by dashed line). Fear responses to subsequent presentations of the conditioned stimulus recover only in healthy participants who encounter the shocks in the same testing context (asterisk indicates $p < 0.05$). Two patients with amnesia (FS and WS, data averaged) acquire and extinguish conditioned SCRs normally but do not show fear recovery, despite being tested in the same context. **c** | Structural MRIs depict selective amygdala damage in patient SM and selective hippocampal damage in patient WS. Panels **a** and **c** (left) modified, with permission, from REF. 111 © (1995) American Association for the Advancement of Science. Panels **b** and **c** (right) modified, with permission, from REF. 117 © (2005) American Psychological Society.

research in humans has confirmed that after conditioned fear responses are extinguished, they can be recovered in a context-dependent manner[117,121,122]. However, amnesic patients with selective hippocampal damage do not show contextual fear reinstatement, despite acquiring fear normally[117] (FIG. 6). Therefore, in the absence of an intact hippocampus, conditioned fear associations can be learned implicitly but are not appropriately retrieved by contextual cues. Interactions among the hippocampus, amygdala and ventromedial PFC are proposed to contribute to the contextual recovery of extinguished fear memories, although the details have not yet been established[110]. In anxiety disorders, contextual factors contribute to fear generalization, traumatic memory retrieval and relapse after exposure therapy[123]. Future work in this area has excellent potential to reveal brain mechanisms that underlie the recovery of latent emotional associations and their contextual control, with direct implications for the treatment of affective disorders.

Imaging fear learning. Brain imaging studies of healthy adults have provided additional insights into the functional anatomy of fear learning. Initial investigations using PET compared blood flow during the habituation and extinction phases of conditioning, as this technique does not have the temporal resolution to differentiate responses to the CS and US during typical training procedures[124,125]. With the advent of event-related fMRI, it became possible to extract haemodynamic signal changes during acquisition training that were transiently elicited by the CS without contamination by signals related to the delivery of the noxious US[126,127]. These and other imaging studies[128–134] have identified a set of brain regions that mediate the acquisition of fear, including the amygdala and periamygdaloid cortex, thalamus, sensory neocortex and anterior cingulate gyrus/medial PFC (FIG. 7).

Angry facial expressions that were subliminally fear-conditioned also engage the amygdala[135] and promote greater functional interactions with the thalamus and superior colliculus than during supraliminal conditioning[136]. Such observations provide indirect evidence for preferential engagement of subcortical pathways to the amygdala during unconscious fear learning. The amygdala's response to conditioned fear stimuli is typically strongest early in acquisition training when the emotional associations are initially formed[126,127], which is

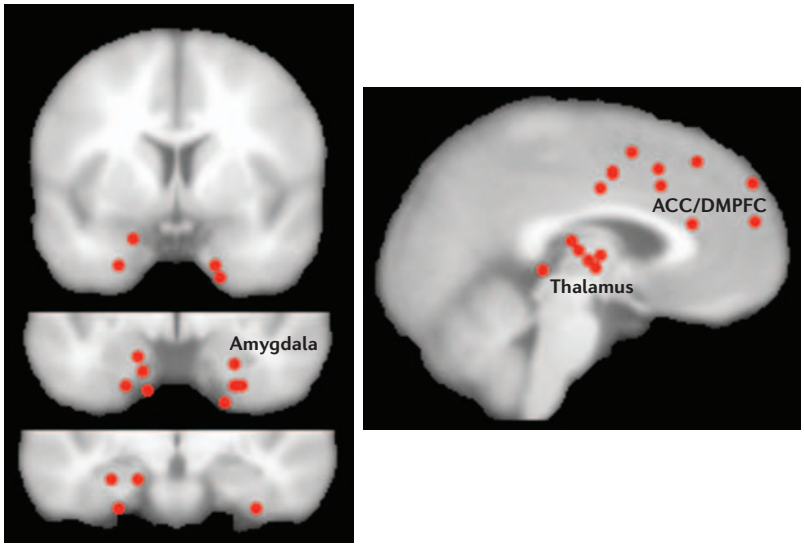

Figure 7 | **Functional neuroimaging of healthy adults during conditioned fear acquisition reveals activation in a thalamo–amygdalo–cingulate network.** Data pooled across nine experiments[124–127,129,131–134] consistently show haemodynamic changes evoked by conditioned fear stimuli in the amygdala and subjacent periamygdaloid cortex (coronal sections, left), and the thalamus and anterior cingulate/dorsomedial prefrontal cortex (ACC/DMPFC, mid-sagittal section, right).

similar to the electrophysiological response profile of some lateral amygdala neurons during fear conditioning in rats[102]. In individual participants, the generation of conditioned SCRs is correlated with CS-evoked activity in the amygdala but not other components of the fear network, which suggests specificity in the link between central and peripheral indices of conditioned learning[127,130,137]. The human amygdala also participates in the extinction of fear[127,131,138] through reciprocal interactions with executive control regions of the medial PFC and anterior cingulate, which suppress fear reactions when they are no longer relevant[138].

Conclusions

Emotion has powerful influences on learning and memory that involve multiple brain systems engaged at different stages of information processing. Studies of declarative emotional memory show how frontotemporal brain regions act conjointly to promote the retention of emotionally arousing events and retrieve them from long-term stores. Memory-enhancing effects of emotional arousal involve interactions between subcortical and cortical structures and engagement of central and peripheral neurohormonal systems that are coordinated by the amygdala. The memory boost conferred by arousal seems to engage similar brain systems across positive and negative valence. By contrast, retention advantages of emotional valence in the absence of high arousal are due in part to frontally mediated semantic and strategic processes that benefit declarative memory without key involvement of the amygdala. The contributions of the amygdala, PFC and MTL memory system extend beyond the initial period of memory consolidation to initiate the retrieval of emotional memories, including those from the personal past. Autobiographical memory research enables ethical assessments of more intense and remote emotional episodes, as well as investigations into emotional influences on the phenomenology of remembering rather than on memory accuracy. Studies of conditioned emotional learning illustrate how the amygdala, PFC and hippocampus make unique contributions to the acquisition, extinction and recovery of fears to specific cues and contexts. Future experiments should characterize more fully the beneficial impact of emotion on other memory systems, including working memory, priming and procedural learning, as well as the detrimental effects of emotion on these systems. During a decade of progress, advances in cognitive neuroscience have begun to unravel the biological mysteries surrounding the persistence of emotional experiences in humans, with implications for understanding memory disturbances in affective disorders.

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