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Human emotion and memory: interactions of the amygdala and hippocampal complex

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The amygdala and hippocampal complex, two medial temporal lobe structures, are linked to two independent memory systems, each with unique characteristic functions. In emotional situations, these two systems interact in subtle but important ways. Specifically, the amygdala can modulate both the encoding and the storage of hippocampal-dependent memories. The hippocampal complex, by forming episodic representations of the emotional significance and interpretation of events, can influence the amygdala response when emotional stimuli are encountered. Although these are independent memory systems, they act in concert when emotion meets memory.

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Abbreviations
fMRI functional magnetic resonance imaging

Introduction

One of the primary advances in the study of memory over the past half century is the growing recognition that there are multiple memory systems that are governed by distinct and interacting neural substrates [1]. Investigations examining the influence of emotion on memory have primarily focused on two medial temporal lobe memory systems (see Figure 1). The first is linked to the amygdala and is more or less specialized for the processing of emotion. The hallmark of this memory system is that it is crucial for the acquisition and expression of fear conditioning, in which a neutral stimulus acquires aversive properties by virtue of being paired with an aversive event. The second is linked to the hippocampal complex and is necessary for declarative or episodic memory. This memory system can be thought of as a primary memory system in humans, in that it governs the function most often referred to as 'memory', that is, the recollection of events at will.

Evidence that these two memory systems are independent comes from patients with focal lesions to the amygdala or hippocampus. In a classic fear conditioning paradigm, during which a neutral blue square is paired with an aversive shock to the wrist, patients with amygdala damage fail to show a normal physiological fear response to the blue square, even though they are able to report that the blue square predicted the shock [2]. Patients with damage to the hippocampus show the opposite pattern [3]. That is, they demonstrate a physiological arousal response to the blue square, but are not able to consciously recollect that it was paired with the shock. This double dissociation highlights the independent functions of these two memory systems. Even though these two systems can operate independently, they also interact in subtle and important ways. In this review, I outline how the amygdala and hippocampal complex influence each other when emotion and memory come together.

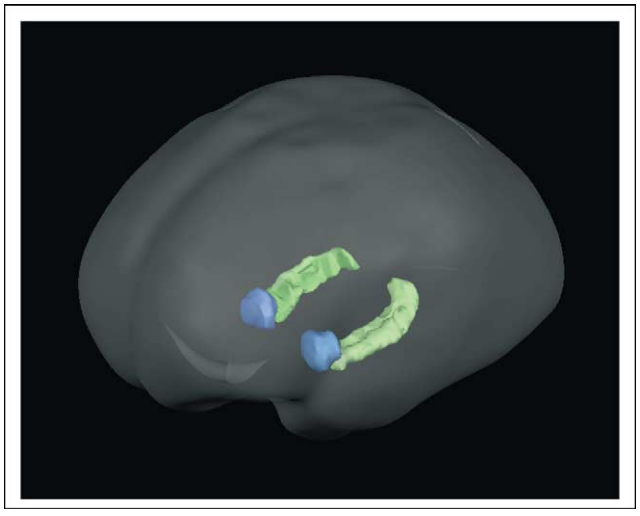
The amygdala's role in hippocampal memory formation

Most research examining amygdala–hippocampal interactions has focused on how the amygdala can influence hippocampal-dependent, episodic memory for emotional stimuli. It is not surprising that there is abundant evidence that memories for emotional events have a persistence and vividness that other memories seem to lack [4]. The question is how does this occur? At least in part, the enhanced memory capability observed for emotional events is due to the amygdala's influence on the encoding and storage of hippocampal-dependent memories.

The amygdala's influence on memory encoding

The first stage of memory is encoding, when a stimulus is encountered for the first time. Although several factors can influence how well a stimulus is encoded, the ability to perceive and attend to the stimulus is a primary factor. Several studies have demonstrated that emotion can influence attention by both capturing attention and altering the ease with which emotional stimuli are processed when attention is limited [5,6]. Using a paradigm called the attentional blink, it was shown that damage to the amygdala impairs the normal facilitation of attention for emotional stimuli [7]. In this paradigm, subjects are asked to selectively attend to two target stimuli (identified by a unique color) presented in a stream of rapidly presented stimuli. When the second target stimulus is presented soon after the first, it is often missed, as if attention 'blinked'. However, if the second target stimulus is arousing, such as a dirty word, subjects are less likely

Figure 1



The human amygdala (in blue) and hippocampus (in green).

to miss it. Put another way, this attentional limitation is attenuated with emotion. Amygdala damage impairs the normal attenuation of the attentional blink effect, which suggests that the amygdala plays a crucial part in the facilitation of attention with emotion.

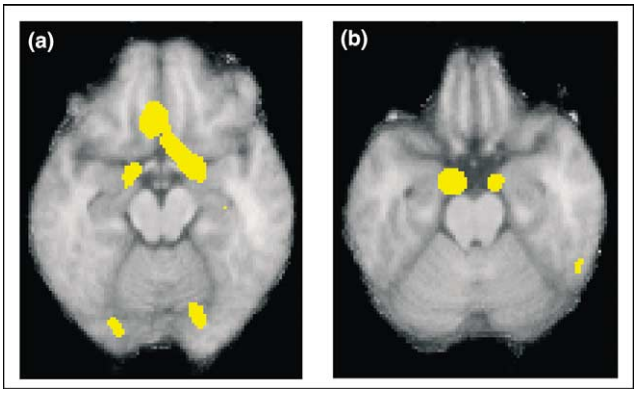
The mechanism underlying the amygdala's influence on attention has been explored recently using functional magnetic resonance imaging (fMRI). The amygdala has reciprocal connections with sensory cortical processing regions, such as the visual cortex [8]. It has been shown that there is an enhanced response in the amygdala to emotional stimuli (i.e. fearful faces) and this response is correlated with a similar response in the visual cortex [8]. The amygdala responds to an emotional stimulus in the environment rapidly [9•], before awareness [10] and, generally, irrespective of attentional focus [11,12••,13]. It has been suggested that the amygdala might receive information about the emotional significance of a stimulus very early in stimulus processing and through feedback connections could enhance later perception, resulting in enhanced perceptual encoding for emotional events. This enhanced perception might underlie emotion's facilitation of attention and the overall increased vigilance observed in the presence of emotional stimuli [14]. By influencing perception and attention, the amygdala can alter the encoding of hippocampal-dependent, episodic memory, such that emotional events receive priority.

The amygdala's modulation of consolidation

The second stage of hippocampal memory formation is retention or storage. There is also evidence that the amygdala can influence the storage of memory. Hippocampal-dependent memories are not stored in an all or none fashion. After encoding, there is a period of time in which these memories are somewhat fragile and prone to disruption. It takes time for these memories to become more or less 'set', at which point their retrieval is less dependent on the hippocampus. This process is called consolidation. It has been suggested that one reason for this slow consolidation process is to allow an emotional reaction to an event an opportunity to influence the storage of that event. The emotional reaction, such as arousal and the release of stress hormones, necessarily follows the event itself [15]. In this way, events that elicit emotional responses, which are likely to be more important for survival, are also more likely to be remembered later. Animal models have suggested that the amygdala modulates the consolidation of hippocampal-dependent memories through the actions of stress hormones. In short, stress hormones activate adrenergic receptors in the basolateral amygdala, which modulates the effect of these hormones on hippocampal consolidation [16••]. In support of these animal models, it has been shown in humans that administering a β-adrenergic blocker eliminates emotion's enhancement of episodic memory [17], as does damage to the amygdala [18,19].

Further support for amygdala involvement in the enhanced long-term memory for emotional events comes from brain imaging studies. Several studies have shown a correlation between activity in the amygdala at encoding and later memory for emotional stimuli (see Figure 2; [20–22]). Although these studies cannot rule out the possibility that the observed memory enhancement is due to the amygdala's influence on attentional or perceptual systems, such as visual cortex, more recent studies have shown a correlation between the amygdala's response to a stimulus and the responses in the parahippocampus, which is part of the hippocampal complex just inferior to the hippocampus proper [23]. In addition, a recent study by Dolan and co-workers [24••] examined

Figure 2



Activation of the amygdala predicts later memory. Amygdala activity during encoding correlated with subsequent memory for **(a)** positive and **(b)** negative arousing picture stimuli. Adapted from Hamann *et al.* [22].

patients with varying degrees of pathology to the hippocampus and amygdala during the encoding of emotional and neutral words. Using fMRI, they found that greater left amygdala pathology predicted both worse subsequent memory for the emotional words and less activity in the left hippocampus. Memory for neutral words was only related to the degree of hippocampal pathology. Interestingly, the relationship between the pathology of the amygdala and hippocampus and the activity in response to emotion words was bi-directional. More left hippocampal pathology predicted less activity in the left amygdala and more activity in the right amygdala, which suggests a mutual dependence of the hippocampus and amygdala when remembering emotional stimuli.

The brain imaging and patient studies cited above support a role for the human amygdala in modulating the hippocampal complex, but do not indicate that this modulation alters the consolidation or storage of memory per se. This question was addressed in two recent studies by Cahill and co-workers. Using a pharmacological [25••] and pain [26] manipulation that elicited a stress hormone response immediately after a target stimulus was encoded, they were able to demonstrate enhanced memory for this stimulus. These results strongly support the conclusion that emotion can alter the retention of emotional events and are consistent with the animal models suggesting a role for the amygdala in the modulation of hippocampal consolidation.

An emerging topic in our efforts to understand the mechanisms underlying the amygdala's influence on emotional memory is the unique roles of the left and right amygdala. Recent brain imaging studies have suggested that the left and right amygdala could be differentially involved in memory for emotional stimuli depending on the sex of the subject. Specifically, two recent studies have shown that the left amygdala is correlated with later memory for emotional stimuli in female subjects, whereas the right amygdala is correlated with memory for emotional stimuli in male subjects [27,28••]. It is unclear if this laterality difference could be related to sex differences in stimulus processing strategies or other factors. However, studies examining emotional memory or physiological responses to emotional stimuli in patients with amygdala damage have failed to find such sex differences. These studies have tended to be consistent with previous studies on hippocampal function showing a material specific involvement of the left and right amygdala for verbal and visual material, respectively [19,29,30]. It is unclear at this time how data from these two different techniques will inform our understanding of the specific roles of the left and right amygdala in episodic memory for emotional events.

In addition to its primary role in the acquisition and physiological expression of conditioned fears, the amygdala has a secondary role influencing the encoding and storage of hippocampal-dependent, episodic memories. This role is modulatory, in that the amygdala is not necessary for forming episodic memories of emotional or neutral events. Rather, the amygdala enhances hippocampal-dependent memory with emotion.

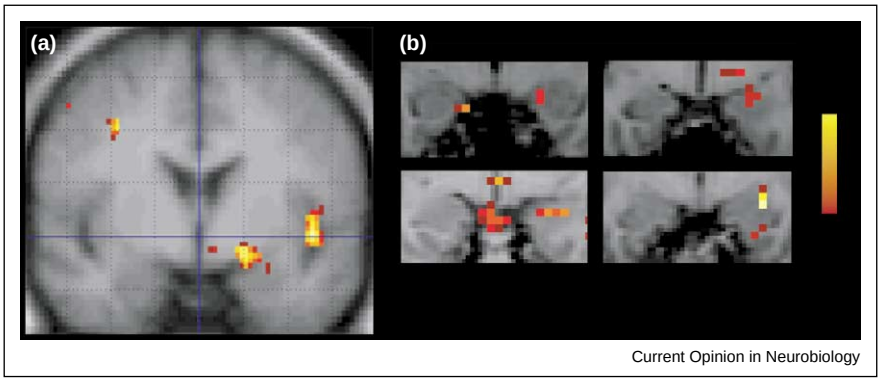
The influence of hippocampal-dependent memory on amygdala function

Although most of the research examining amygdala–hippocampal interactions has explored how the amygdala can influence episodic memory, there is also evidence of episodic memory influencing the amygdala. In the typical fear conditioning paradigm, a subject learns that a neutral stimulus predicts an aversive event by virtue of their pairing. In everyday human experience this type of learning often occurs. For example, if you were bitten by a neighborhood dog, the next time you encounter this dog you might have a fear response. This is an everyday example of fear conditioning. However, for humans it is also possible to learn about the emotional significance of stimuli in the environment through other means, such as verbal communication. You might have a similar fear response to the neighborhood dog if your neighbor had previously told that it was a dangerous dog that might bite you. This type of learning through instruction requires the hippocampal complex for acquisition and, possibly, for retrieval when the fearful stimulus is present. Through instruction, subjects can acquire an episodic representation of the emotional significance of an event without any direct aversive experience. The question is, does this hippocampal-dependent, episodic representation of emotional significance influence the amygdala?

In an fMRI study, subjects were told that they would receive one or more mild shocks to the wrist, but only when a blue square was presented. Although no shocks were actually presented, subjects showed an arousal response during presentation of the blue square as well as activation of the left amygdala (see Figure 3; [31]). A similar study found that damage to the left amygdala impaired the physiological fear response to the blue square [29]. These results suggest that having an instructed, episodic representation of the emotional significance of a stimulus can lead to activation of the amygdala, which in turn mediates the physiological expression of fear when this stimulus is encountered. These types of fears are imagined and anticipated, but never actually experienced, yet they rely on similar neural mechanisms for expression as those that are learned through direct experience.

Another example of hippocampal-dependent, episodic representations influencing amygdala function comes from recent studies on emotion regulation [32••,33]. Our ability to regulate our emotional responses is an important part of normal social behavior. Studies examining the neural systems of emotion regulation instruct

Figure 3



Amygdala activation to an episodic representation of fear. Left amygdala activation to instructed fear. Composite activation response to **(a)** threat versus safe stimuli and **(b)** selected individual subjects. Adapted from Phelps *et al.* [31].

subjects to use strategies to alter their response to emotional stimuli. A recent fMRI study instructed subjects to 'reappraise' the emotional significance of a negative scene by trying to interpret the events depicted in a non-emotional or positive light [32••]. Both the acquisition and the appropriate application of this strategy require hippocampal-dependent memory. The reappraisal strategy was successful in diminishing both the reported emotional reaction to the negative scenes and the amygdala response.

The recollection of emotional stimulus properties and strategies acquired through instruction requires the formation of hippocampal-dependent memories. These episodic memories can influence our emotional reactions, at least in part by modulating the amygdala.

Conclusions

The amygdala and hippocampal complex govern two independent memory systems that interact when emotion meets memory. We are just beginning to understand the subtleties of these interactions in humans and there are still several unanswered questions.

Although we know more about the mechanisms that underlie the amygdala's influence on hippocampal-dependent episodic memory, it is not clear how the modulation of attention and encoding complements the modulation of consolidation. It has been suggested that the amygdala primarily enhances episodic memory for the gist of an emotional event at the expense of details [34], which may be related to attention. It has also been suggested that this gist versus peripheral detail memory enhancement might interact with sex and laterality when memories are consolidated [35]. Researchers are only beginning to investigate these topics and it is unclear which, if any, of these factors will prove to be important.

In addition, a recent fMRI study suggested that the relationship between the amygdala and the hippocampus might be bi-directional during the encoding of emotional events [24••]. Exactly what role hippocampal feedback to the amygdala might play in the enhancement of episodic memory with emotion is not known.

It is clear that episodic memory plays a part in our representation of emotion and this can influence the amygdala [31]. However, very little is known about exactly how an episodic representation alters amygdala function. This is partially due to the fact that we have a relatively poor understanding of the precise mechanisms of storage for hippocampal-dependent memories in general, although it is likely that working memory plays an important part when an episodic memory is retrieved. A recent fMRI study on emotion regulation [32••] suggested that areas typically linked to working memory are involved when instructed strategies are applied and the amygdala response is modulated.

Until recently, emotion was not typically considered in our efforts to understand cognitive behaviors, such as memory. However, it has become increasingly clear that we can no longer neglect the exploration of emotion, as it is rarely absent from our daily functions. In this review, we have highlighted what has been learned from investigations into the neural systems of emotion and memory in humans thus far, which has often relied on animal models as a guide. We are just starting to explore more complex interactions between emotion and memory that could be unique to human function.

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