Emotional memory

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We remember life's important moments especially well. Emotional experiences, whether good or bad, leave strong traces in the brain. It was once thought that there was a single memory system in the brain. Now, however, we know that memories are formed in a variety of systems that can roughly be divided into two broad categories: systems that support conscious memory (i.e. explicit memory systems) and systems that store information unconsciously (i.e. implicit memory systems). Memories about emotional situations are often stored in both kinds of systems (Figure 1).

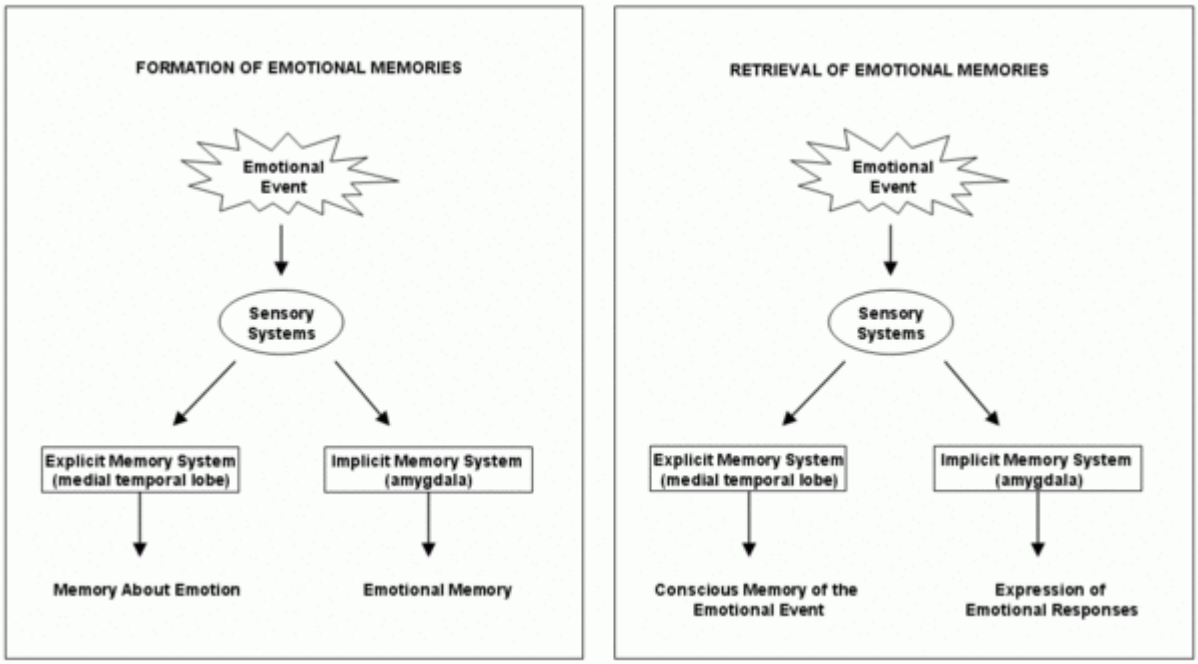

Figure 1: Emotional Memories vs. Memories About Emotions. Left: Formation of emotional memories. Emotional events are processed in sensory systems and then transmitted to the medial temporal lobe for the formation of an explicit memory about the emotional situation and to the amygdala for the formation of an emotional memory. When a cue from the memory occurs and is processed by the sensory system, it leads to the retrieval of a conscious memory about the emotional event in the medial temporal lobe but leads to the expression of emotional responses when retrieved in the amygdala.

Implicit Emotional Memory Is Best Understood Through Studies of Pavlovian Fear Conditioning

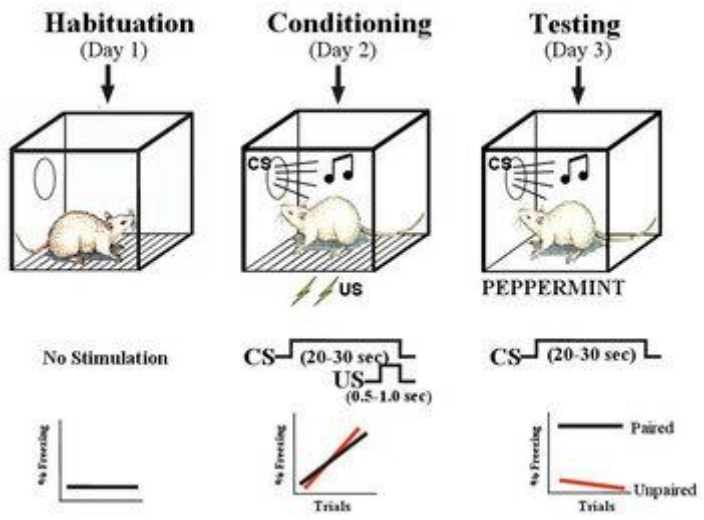

Figure 2: Fear Conditioning. Fear conditioning occurs in three phases. In habituation the rat is acclimated to the chamber. No stimuli are presented. During conditioning the tone conditioned stimulus (CS) is paired with the footshock unconditioned stimulus (US). Testing then involves presentation of the CS without the US the next day. Typically, the rat exhibits freeing responses to the CS during the test. If the rats received unpaired presentations of the CS and US during conditioning, they freeze little to the CS, indicating that they did not come to associate the CS with the US.

Much of our understanding of the neural systems that process and respond to emotional stimuli has come from studies utilizing Pavlovian fear conditioning as a behavioral paradigm (Figure 2). In fear conditioning, the subject receives a neutral conditioned stimulus (CS), usually a tone, followed by an aversive unconditioned stimulus (US), typically footshock. After one or at most a few pairings, the CS comes to elicit conditioned emotional responses that naturally occur in the presence of threatening stimuli, such as predators. Conditioned emotional responses include changes in behavioral, autonomic nervous system (ANS), and hormonal activity elicited by the CS after conditioning compared to before. Fear conditioning has been used to study the brain mechanisms of learning and memory in both animals and humans. In humans, ANS responses are typically measurable. The CS elicits ANS responses in humans even when it is masked, and thus prevented from entering conscious awareness, during either conditioning or testing. This indicates that fear conditioning is an implicit form of learning and memory.

The circuitry underlying fear conditioning has been mapped in considerable detail (Figure 3). Pathways processing the CS (auditory pathways) and US (pain pathways) converge in the lateral nucleus of the amygdala (LA), and several other regions. CS-US convergence in the LA initiates synaptic plasticity, leading to the formation of a learned association between the two stimuli. When the CS occurs at some later time, it retrieves the associative memory in the LA.

Activity in LA is then transmitted to the central amygdala, which then connects to hypothalamic and brainstem areas that control behavioral, ANS, and hormonal responses that help the organism cope with the threat. Plasticity occurs in other regions of the amygdala, such as the basal and central nuclei. Whether these changes depend on the lateral nucleus or might be independent is debated.

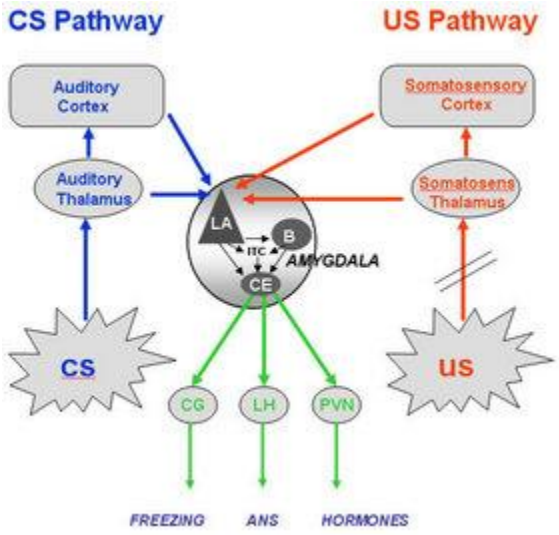

Figure 3: Neural Circuit of Fear Conditioning. Fear conditioning occurs in the brain via the modification of the processing of the auditory conditioned stimulus by the somatosensory unconditioned stimulus. As shown, the CS and US converge in the lateral amygdala (LA), which receives CS and US inputs from both thalamicand cortical areas. The LA then communicates with the central amygdala (CE) both directly and by way of other amygdala areas, including the basal nucleus (B) and the intercalated masses (ITC). The CE connects with brainstem and hypothalamic areas that control the expression of fear responses, including freezing behavior (mediated by the central gray, CG), autonomic nervous system (ANS) responses (mediated by the lateral hypothalamus, LH), and hormonal responses (mediated by the paraventricular hypothalamus).

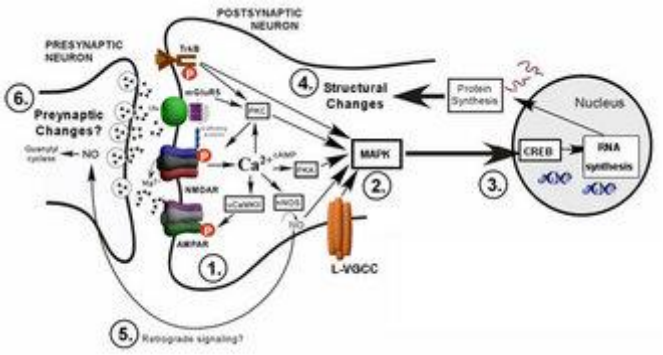

Figure 4: A Model of Fear Memory Consolidation in the Lateral Amygdala (LA). (1) Acquisition and short-term memory (STM) formation of fear conditioning requires events at the post-synaptic density, including activation of NMDA receptors, metabotropic glutamate receptors (mGluR5), calcium calmodulin kinase (CaMKII), and,

possibly protein kinase C (PKC). Both CaMKII and PKC may contribute to STM by influencing the conductance of NMDARs and AMPA receptors. (2) Long-term memory (LTM) formation of fear conditioning requires the activation of TrkB receptors, L-type voltage gated calcium channels (VGCCs), and the cyclic AMP (cAMP)-protien kinase A (PKA) signaling pathway. Each of these pathways is thought to converge on ERK, which is thought to promote long-term memory and synaptic plasticity by translocating to the nucleus to influence gene expression. (3) CREB and CRE-mediated transcription are both required for LTM of fear conditioning. (4) The translation of CRE-mediated genes into proteins may lead to structural changes at LA spines that contribute to the permanence of LTM formation. (5). The activation of nNOS in LA neurons may promote retrograde signaling by NO and structural and/or functional changes on the presynaptic side of the synapse (6). Illustration and caption courtesy of Glenn Schafe, Deparment of Psychology, Yale University.

The molecular mechanisms of plasticity in the LA have been studied extensively using both pharmacological manipulations during fear conditioning and through studies of long-term potentiation, a cellular model of learning (Figure 4). Both approaches indicate that plasticity in LA depends on calcium entry through NMDA receptors and voltage gated calcium channels. The elevated calcium triggers a number of intracellular cascades involving kinase mediated enzymatic reactions. Particularly important are CamKII, PKA, and MAPK. These lead to gene expression in the cell nucleus and protein synthesis. Memory is maintained by insertion of new AMPA receptors and possibly structural changes.

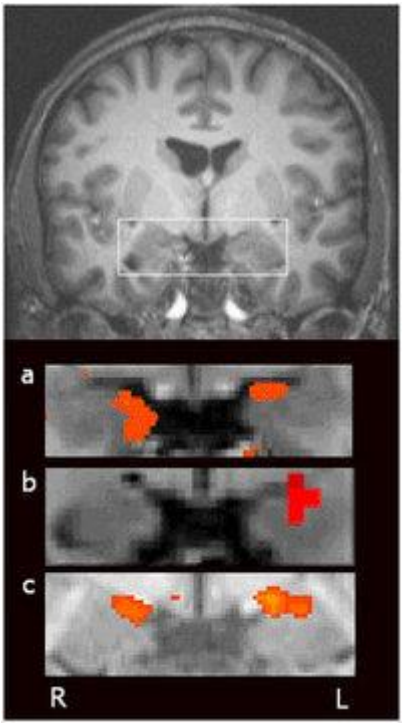

Figure 5: Conditioned Fear in the Human Brain. Above: structural magnetic resonanceimage (MRI) of the human brain. The area containing the amygdala is within the box. (a) Fear Conditioning. Functional MRI(fMRI) showing amygdala activation by a conditioned stimulus (CS) after pairing with an unconditioned stimulus; (b) Instructed

Fear. fMRI showing amygdala activation by a CS that was not directly paired with a US but instead the subjects were instructed unconditioned stimulus; (c) Observational Fear Learning. fMRI showing amygdala activation by a CS after the subjects observed someone else undergoing fear conditioning where the CS was paired with a US. Illustration and caption courtesy of Elizabeth Phelps, Deparment of Psychology, NYU.

Research in humans has confirmed the essential role of the amygdala in fear conditioning (Figure 5). Thus, damage to the amygdala in humans prevents fear conditioning from occurring, as measured by autonomic nervous system (ANS) responses and functional imaging studies showing that CS-elicitied activity increases in the amygdala during fear conditioning and the level of activity is correlated with the magnitude of ANS responses elicited by the CS. Amygdala activation also occurs when stimuli are masked, indicating that CS-elicited amygdala activity, like CS-elicited ANS responses, occurs in the absence of awareness of the CS and its relation to the US. Amygdala activation and ANS responses also occurs to masked emotional faces. These unconditioned responses add further evidence that the amygdala engages in implicit emotional processing. Thus, both conditioned and unconditioned emotional stimuli elicit activity in the amygdala and autonomic nervous system responses independent of conscious awareness of the stimulus.

It should be emphasized that the amygdala does not function alone in the mediation of fear conditioning (Figure 6). It is part of a larger circuitry involving not only sensory input systems and motor output systems but also systems that contribute to the processing of contextual stimuli (areas of the hippocampus) and in the regulation of amygdala reactivity (prefrontal cortex). The amygdala has also been implicated in processing positive emotional stimuli. However, less is known about this circuitry.

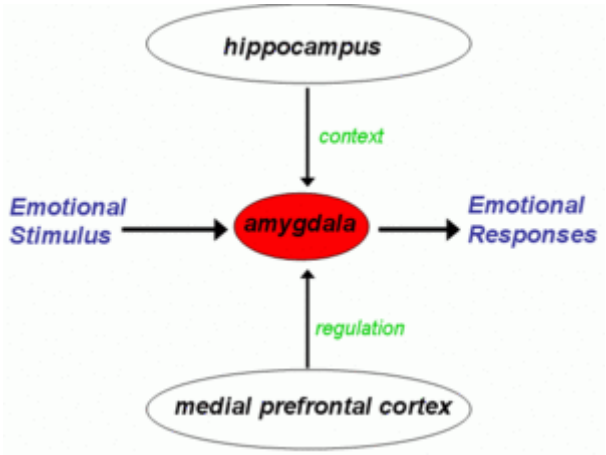

Figure 6: Partners in Fear. The amygdala's ability to control fear responses to threatening stimuli is regulated by the hippocampus and medial prefrontal cortex. The hippocampus adds contextual regulation, allowing you to

distinguish the difference in threat level posed by a snake in the woods vs. in a zoo. The medial prefrontal cortex regulates the degree to which the amygdala expresses fear responses.

Explicit Emotional Memory Involves the Medial Temporal Lobe Memory System

Studies in the 1950s found that damage to the medial temporal lobe (MTL), especially the hippocampus and related cortical areas, in humans leads to profound deficits in the ability to store new memories. Initially thought of as a global memory disorder, the memory deficit produced by MTL damage came to be understood as one involving explicit memory, memory that is stored in a way that allows retrieval into conscious awareness. Explicit memory involves both memory for facts (semantic memory) and memory for personal experiences (episodic memory). Both forms of explicit memory depend on the MTL, though it is possible that different subregions make unique contributions to semantic and episodic memory. Traditionally, it was believed that explicit memory is gradually transferred from the hippocampus to other cortical areas over time. More recently, though, some have proposed that this lack of involvement of the hippocampus in memory over time is more apparent than real—that memories stored in the hippocampus always depend on this structure. Like the role of different subegions of the MTL in the formation of explicit memory, the role of the hippocampus in the storage of explicit memory will have to be resolved by additional research. Just as the amygdala is involved in implicit emotional memory, the hippocampus is involved in explicit memory about emotional situations (Figure 1). Thus, when emotionally aroused we form semantic and episodic memories about such situations. These, though, are cognitive representations of emotional situations better referred to as memories about emotions rather than emotional memories.

Implicit Activation of the Amygdala Can Modulate Explicit Memory Storage

Emotional arousal often leads to stronger memories (Figure 6). This is a statement about explicit memories involving emotional situations (memories about emotions). The statement is unquestionably true, but there are two important caveats. First, while emotional experiences often produce very powerful and vivid memories that are easily recollected, the memories are not more accurate in their details than non-emotional memories. The confidence we have in memories about emotional events is thus not always to be trusted. Second, a loss of explicit memory, an amnesia, can also occur for intense emotionally charged situations.

The effects of emotional arousal on explicit memory are due to processes that are secondary to the activation of emotional processing systems in the brain. For example, in a situation of danger, processing of threatening environment stimuli leads to activation of the amygdala,

which in turn transmits information to networks in the hypothalamus and brainstem. Activity in these areas then leads to increases in brain arousal (due to activation of modulatory systems that lead to the release of neurochemicals such as norepinephrine and acetylcholine throughout the brain) and to the expression of behavioral, autonomic and endocrine responses.

Connections from the amygdala to networks containing neuromodulators are important in regulating brain arousal during emotional situations. Thus, connections to the brainstem neurons containing norepinephrine, dopamine, serotonin, and acetylcholine lead these neurons to release their chemicals in widespread areas, including areas involved in forming and storing explicit memories. These chemicals thus facilitate the formation of memories about emotions.

Connections from the amygdala to the paraventricular hypothalamus (either direct or indirectly through other areas) lead to the release of ACTH from the pituitary gland. ACTH then circulates to the adrenal gland in the kidneys where it stimulates the release of glucocorticoid hormone (CORT) from the adrenal cortex (corticosterone in rats, cortisol in humans). CORT has complex effects on memory. In mildly stressful situations, low or intermediate levels of circulating CORT enhance explicit memory formation by way of actions in the hippocampus. With prolonged and intense stress, higher levels of circulating CORT over an extended period can lead to the impairment of explicit memory. Prolonged exposure to glucocorticoids is known to impair physiological functions of the hippocampus. Traditionally, memory failure following trauma has been attributed to memory repression, but at least some instances of repression may be due to glucocorticoid induced amnesia.

Connections from the amygdala to brainstem areas controlling the autonomic nervous system (ANS) lead to the activation of the sympathetic division of the ANS. As a result, epinephrine and norepinephrine are released into the circulation from the adrenal medulla. These do not cross the blood brain barrier. Instead they act on peripheral nerves that project into the brain. For example, it is believed that the memory enhancing effects of epinephrine on memory are due to a direct action on the peripheral nerve endings of the sensory component of the vagus nerve. This nerve then innervates areas in the brainstem that ultimately connect with the locus coeruleus, which then releases norepinephrine in the amygdala, hippocampus and other forebrain areas. Through these channels, perpipheral catecholamines such as epinephrine and norepinephrine can alter the strength of explicit memory. Damage to the amygdala prevents these modulatory effects on explicit memory.

Conclusion

Much has been learned about the formation of implicit emotional memories and how arousal by learned or unlearned emotional stimuli can affect the storage and retrieval of information in the explicit memory system. Most of what we know at this point is based on aversive emotional states modeled by Pavlovian fear conditioning. It is likely that many of the principles at the systems, cellular, and molecular level will apply to other forms of emotional learning, but this remains to be determined.

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