

The Amygdala, the Hippocampus, and Emotional Modulation of Memory

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There are two views regarding the role of the amygdala in emotional memory formation. According to one view, the amygdala modulates memory-related processes in other brain regions, such as the hippocampus. According to the other, the amygdala is a site for some aspects of emotional memory. Here the authors adduce behavioral, electrophysiological, and biochemical evidence in support of an integrative view, assuming both roles for the amygdala. This integrative view, however, suggests a level of complexity not referred to before: the assumption that emotional conditions induce long-term neural plasticity in the amygdala suggests that the interrelations between the amygdala and brain regions, such as the hippocampus, may not be static but dynamic. The way the amygdala will affect memory-related processes in the hippocampus may thus largely depend on the previous history of the individual. *NEUROSCIENTIST* 10(1):31–39, 2004. DOI: 10.1177/1073858403259955

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The hippocampus is considered to play a central role in the formation of explicit/declarative types of memories. These are described in humans as the conscious recall of past events, and in animals as processing of spatial, configural, contextual, and relational information. The hippocampus receives information from all regions of the association cortex and the cingulate cortex via the pirrhinal cortex, which projects to the entorhinal cortex (EC). The EC receives further inputs from subcortical regions, such as the amygdala, and projects to the hippocampal formation. Further subcortical modulation reaches the hippocampus via the fornix. Thus, the hippocampus, via its neural connections, is well situated to put a specific event into its proper context; it binds together multiple events that co-occur during an experience, and through this kind of rich processing, it converts short-term into long-term memories and allows accurate episodic memories to be formed (Chiba and others 1994).

Attending to our daily affairs we are constantly exposed to an endless stream of sensory information. At any given moment, sights, voices, odors, or tastes infiltrate our brain and initiate neural activity. Eventually, however, only a handful of these stimuli are registered into our long-term memory. Indeed, constantly receiving a vast amount of information, an effective memory system, such as the hippocampal formation, quickly and efficiently has to learn to distinguish the more important

from the less important stimuli and to transform only the former into long-term memory. What might help it to decide what is important, and therefore should be retained, and what is less relevant? One possible factor that could guide the hippocampus is the emotional load of the experience. Arousal caused by an emotional experience could tag a salient event and promote facilitation of its consolidation. Indeed, it seems that emotionally aroused events are better remembered than neutral events, which are generally weakly retained or require repetition to endure. Indeed, it has been suggested that emotional arousal has a key role in the enhancement of memories for significant information (McGaugh 2000).

The Emotional Tagging Concept

The emotional load of the experience may induce a general, nonspecific arousal effect that would enhance attention and thus support the establishment of long-term memory. This effect is sufficient to explain in part emotional influences on memory formation. Recently, however, we hypothesized an additional and more specific role for the emotional cues in helping to sift the more relevant from the less relevant aspects of an experience, in order to transfer only significant events into long-term memory. We suggest that neuromediators, activated by the emotional load of the experience, are able to modulate memory-related processes in brain areas such as the hippocampus and to enhance consolidation. An enhanced memory may be more persistent (i.e., long-lasting), stronger (i.e., resistant to disruptions), or more accurate, or a combination of the above. This ability of the emotional aspects of the experience to modulate information into enhanced memories by strengthening neuro-plasticity in brain regions such as

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the hippocampus is what we refer to as *Emotional Tagging* (Richter-Levin and Akirav 2003).

If the Emotional Tagging Hypothesis is correct, the information about the emotional load of an experience should be able to reach memory systems such as the hippocampal formation and to affect memory-related processes in these regions. To assess this possibility, several laboratories have embarked on studying the effects of an emotional experience on memory-related processes in the hippocampus. Mostly, studies focused on the effects of aversive, stressful experiences on memory-related processes.

Neural Plasticity in the Hippocampus

Searching for the neural mechanisms underlying learning has led to the widely accepted notion that altering the efficacy of communication between nerve cells has a pivotal role in learning and memory formation. More than 50 years ago, the Canadian psychologist Donald O. Hebb postulated an experience-dependent way of modulating the efficacy of communication between nerve cells. He suggested that when a presynaptic neuron persistently takes part in activating a postsynaptic neuron, the efficacy of communication between them will increase. Searching for a Hebbian-type modulation of the efficacy of neuronal communication in the mammalian brain, Bliss and Lomo (1973) discovered that applying a brief, high-frequency stimulation to the excitatory afferent pathways of the hippocampus could lead to an enduring increase in the magnitude of the neurons' response. This phenomenon, later termed long-term potentiation (LTP), is long-lasting. In freely moving animals, in which the response can be monitored for days, LTP was found to last for days and even months (Abraham and others 2002). It is important to note that the artificial stimulation of the afferent fibers does not directly activate the cells but rather mimics activity-induced action potentials. The activation of the cells in the hippocampus in this preparation is the result of activation of the incoming synapses and of the release of neurotransmitter. In this respect, LTP is justifiably referred to as an activity-dependent form of synaptic plasticity. Furthermore, several patterns of stimulation, such as primed-burst (PB) and theta-burst stimulation, were found to be as effective as the initial high-frequency pattern of stimulation in inducing LTP (Diamond and others 1988; Pavlides and others 1988).

In addition to its enduring nature, other properties of LTP, such as synaptic specificity, associativity, and cooperativity, were described, which well suited the notion of a memory formation mechanism. But like memory processes, LTP is not a unitary process. The most informative distinction so far has been made between NMDA-dependent and NMDA-independent LTP. Regardless of these differences, LTP, like memory, was found to consist of at least two distinctive stages. A short-term LTP (S-LTP), which lasts for about 2 to 3 hours, and then, if stimulation was effective enough, a long-term LTP (L-LTP) will develop. L-LTP may last for

hours or days. Importantly, L-LTP differs from S-LTP in that it requires the activation of protein synthesis (Matthies and others 1990). As with short- and long-term memory, blocking protein synthesis will block L-LTP but not S-LTP (Nguyen and others 1994).

Stress, the Hippocampus and LTP

All living organisms experience stressful events during their lifetime. Physical and psychological stressors provoke the secretion of the catecholamines epinephrine and norepinephrine (NE), and of the glucocorticoids (GLUC) (McEwen and Sapolsky 1995).

Brief periods of stress can potentiate memory formation, whereas more severe or prolonged stress can have deleterious effects upon broad aspects of cognition (McEwen and Sapolsky 1995). It has been suggested that the effects of stress, in particular of glucocorticoids, on memory are mediated through their influence on the hippocampus.

One of the best-characterized effects is the capacity of psychological stress and stress-induced levels of glucocorticoids to disrupt LTP and primed-burst potentiation (PBP) (Fig. 1). Numerous studies, using a broad range of stressors (novelty, restraint, shock, predator exposure), have consistently shown that stress or elevated levels of corticosterone inhibit the induction of excitatory plasticity (LTP and PBP) and promote the induction of inhibitory plasticity (long-term depression: LTD) in the hippocampus (e.g., Foy and others 1987; Diamond and others 1992; Pavlides and others 1993; Xu and others 1998; Akirav and Richter-Levin 1999; Mauron and Richter-Levin 2003). In addition to affecting synaptic plasticity and memory, stress and corticosterone have been shown to alter hippocampal dendritic morphology and inhibit neurogenesis in the adult brain, which can also have an impact on memory-related functioning (for review, see Kim and Diamond 2002).

Nevertheless, lower concentrations of corticosterone, such as those that occur naturally during the diurnal rise, enhance such plasticity (Diamond and others 1992). This dissociation between the effects of basal and stress levels of this hormone corresponds to the two types of receptors for glucocorticoids that are abundant in the hippocampus (McEwen and Sapolsky 1995). The high-affinity type 1 receptors (mineralocorticoid receptors; MR) are heavily occupied by basal levels of adrenal steroids during the diurnal cycle, whereas elevation of glucocorticoid concentrations into the stress range increases the occupation of the lower-affinity type 2 receptors (glucocorticoid receptors; GR).

Evidence from behavioral paradigms also shows that stress and/or corticosterone modulates the ability of the hippocampus to store and retrieve information in an inverted U-shaped function (Fig. 2). For example, a high dose of corticosterone or GR agonist 2 h prior to training in the Y maze resulted in impaired spatial memory (Conrad and others 1997). Similar results were seen in retrieval: inducing a foot shock or corticosterone administration 30 min before a retention test for the spatial task

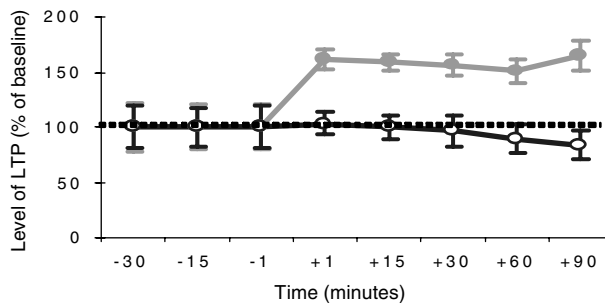


Fig. 1. A representative example of stress effects on the ability to induce LTP in CA1 area of the hippocampus. In anaesthetized control rats (filled circles), LTP was readily induced and lasted for over an hour. In contrast, the ability to induce LTP in rats that were exposed to a stressor (empty circles; elevated platform stress in this case) was significantly reduced. Similar findings were reported from several laboratories (see text for details).

in the water maze impaired retention (de Quervain and others 1998), and placing rats near a cat, which evokes an intense fear response in the rats, impaired their memory for recently acquired spatial information (Diamond and others 1996).

However, a different picture emerges when evaluating the effects of the stress reaction that is elicited during a learning situation. Several studies have shown a facilitative role for training-induced corticosterone release on the neural mechanisms determining the strength of memory storage. It has been shown that although water maze spatial training at 19°C is associated with higher levels of corticosterone (compared with training at 25°C), 19°C-trained rats showed better long-term memory than those trained at 25°C (Sandi and others 1997). Moreover, the removal of endogenous corticosterone impairs performance, adrenalectomy (ADX) or injecting a GR antagonist impairs performance in a spatial learning task (Oitzl and de Kloet 1992), and rats injected with GR antagonist 1 h prior to or immediately after contextual fear conditioning displayed less contextual fear conditioning (considered to be hippocampus-dependent) than rats injected with vehicle (Pugh and others 1997).

The Amygdala and Emotional Memory

The specific role of the amygdala in memory formation has been a topic of debate. There is an agreement that the amygdala is involved in the storage of emotionally arousing events such as those that evoke fear. However, whether the amygdala serves as the site of long-term emotional memory storage, or whether it modulates memory consolidation in other brain areas, is a matter in dispute (Cahill and others 1999; Fanselow and LeDoux 1999).

In recent years, while studying the role of the amygdala in the formation of memory and in particular of emotional memory, we were able to produce evidence to support both views. In the present review, we first describe evidence for a role of the amygdala in modulating memory formation in the hippocampus. We then present evidence to support a role for the amygdala in

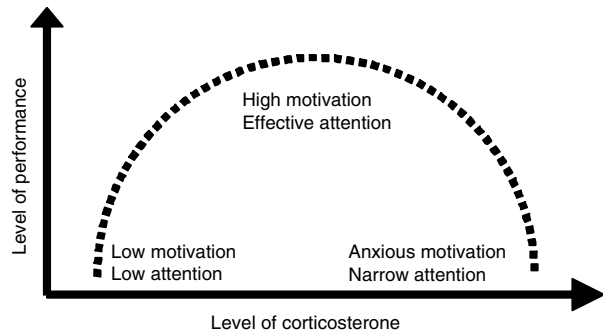


Fig. 2. The proposed inverted U-shaped function of the stress hormones effects of performance in memory tasks may be related to motivational and attentional processes. The lower performance associated with very low levels of stress is usually explained by the low motivation that accompanies the low stress and the ease with which the subject is therefore diverted from one's objective. During intermediate stress levels, the level of motivation to solve the problem reaches the optimum zone in which the stress broadens the span of attention so that the subject is more amenable to relevant information. Under high levels of stress, on the other hand, it may be that the motivation to solve the task is so high that the subject's perception narrows to only very prominent cues, ignoring other, potentially important information.

holding some aspects of the formed memory. Finally, we discuss the functional consequences of such a dual role for the amygdala in emotional memory.

Amygdala Modulation of Memory-Related Processes in the Hippocampus

The assumption that the amygdala modulates hippocampal memory storage is rooted in several lines of research at the anatomical, the electrophysiological, and the functional levels.

Anatomically, There Are Projections from the Amygdala to the Hippocampus

The most widespread projections from the amygdala to the hippocampal formation originate in the basal nucleus, which projects substantially to the EC, CA3, and CA1 fields of the hippocampus, the subiculum, and the parasubiculum (the EC and the parasubiculum then project to the DG). The accessory basal nucleus projects substantially to the EC, the CA1 field, and the parasubiculum. The main projections from the lateral nucleus are directed to the EC and the parasubiculum (Pikkarainen and others 1999).

Electrophysiological Findings

Because behavioral stressors impair LTP, it was expected that the activation of the amygdala, which is assumed to mediate some aspects of stress, would also impair LTP. Yet others (see review by Abe 2001) and we (Akirav and Richter-Levin 1999) have found the contrary. However, the behavioral stressors that were found to impair LTP were applied some time (often 1 h or more) prior to the activation of the hippocampus, whereas BLA

priming in the experiments above was applied only seconds prior to the activation of the hippocampus. When we evened the temporal profile of the behavioral and electrophysiological procedures by activating the BLA 1-2 h before applying HFS to the hippocampus, hippocampal LTP was significantly suppressed, similarly to the suppression seen by the behavioral stressor (Akirav and Richter-Levin 1999, 2002). Moreover, when we combined the behavioral stressor with BLA priming, for example, exposed animals to the behavioral stressors and 1 h afterward primed the BLA, there was no enhancement of hippocampal LTP. Hence, the exposure to the stressor completely blocked the enhancing effect of BLA priming on hippocampal LTP.

These results led us to suggest that the amygdala has a bi-phasic effect on hippocampus-dependent plasticity (Fig. 3): a fast excitatory phase, which results in the enhancement of hippocampal plasticity, and a slow inhibitory phase, which suppresses hippocampal plasticity. We suggested that through the excitatory phase the amygdala “marks” emotionally charged experiences as important by strengthening of synapses located on hippocampal neurons that have just been activated due to the learning experience (Richter-Levin and Akirav 2000). As noted, we termed this enhancement of memories by amygdalar modulation “emotional tagging” (Richter-Levin and Akirav 2003). The slower inhibitory phase, on the other hand, may be beneficial in reducing masking effects of subsequent, less significant events during the initial stages of consolidation.

Functional Indications for Amygdala Modulation of Hippocampal Functioning

Behavioral pharmacology experiments showed that post-training intra-amygdala infusions of different neuromodulatory systems influenced the memory for different hippocampus-dependent tasks; for example, posttraining intra-amygdala infusions of amphetamine-enhanced memory in both spatial and cued training water maze tasks, which are known to be dependent on the hippocampus and the caudate nucleus, respectively (Packard and others 1994). Posttraining muscarinic cholinergic receptor activation of the BLA enhanced contextual fear conditioning, and posttraining intra-BLA infusions of NE enhanced retention for the location of the hidden platform in a spatial water maze task (McGaugh 2000). Furthermore, intra-amygdala injection of NMDA induced c-fos expression in the dorsal hippocampus.

BLA lesions were also found to have an effect on hippocampus-dependent learning. BLA lesions blocked the memory-modulating effects induced by a GR agonist infused into the hippocampus as well as memory impairment induced by either adrenalectomy or intrahippocampal infusions of a GR antagonist (for review, see Roozendaal 2000). Lesions of the stria terminalis (a major afferent/efferent pathway of the amygdala) were found to attenuate the effects of posttraining intra-amyg-

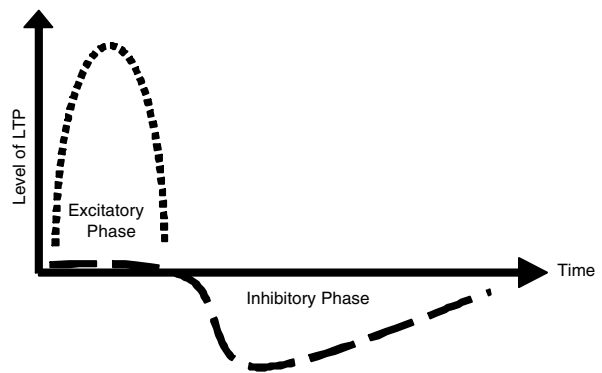


Fig. 3. Activating the amygdala prior to perforant path (PP) stimulation has a biphasic effect on LTP in the dentate gyrus of the hippocampal formation; priming the basolateral amygdala (BLA) immediately prior to PP tetanization results in the enhancement of LTP, whereas spaced BLA stimulation (i.e., activating the amygdala 1–2 hours prior to tetanization of the PP) results in LTP suppression. We suggested that the fast excitatory phase may serve as a marker that generates strong memories for emotionally charged experiences (an “emotional tag”) and that the slower inhibitory phase may be beneficial in reducing masking effects of subsequent, less-significant events during the initial stages of consolidation (for review, see Richter-Levin and Akirav 2003).

dala drug treatments on hippocampus-dependent memory tasks (McGaugh 2000).

Amygdala Modulation of Hippocampal Activity Is Mediated by Stress Hormones

The effects of the amygdala on hippocampus-dependent tasks were suggested to be mediated by the stress hormones NE and glucocorticoids (GLUC).

Lesions of the amygdala or the ST blocked epinephrine effects on memory storage (McGaugh 2000). In addition, NE release in the amygdala was found to be involved in mediating epinephrine effects on memory; posttraining intra-amygdala infusions of NE or beta-adrenoceptor agonist produced dose-dependent enhancement of memory storage for several tasks including spatial tasks (McGaugh 2000), whereas posttraining intra-amygdala infusions of beta-adrenoceptor antagonists impaired retention and blocked the memory-enhancing effects of NE (McGaugh 2000).

Similarly, an intact BLA is necessary for systemically administered GLUC to modulate memory formation (for review, see Roozendaal 2000). Lesions of the amygdala or the ST blocked the memory-enhancing effects of posttraining systemic injections of GLUC or GR agonists, and the impairing effects of ADX or ICV administration of GR antagonists in a spatial task in the water maze. BLA lesions also blocked the memory-enhancing effects of posttraining intrahippocampal injections of CORT or GR agonist and the impairing effects of a GR antagonist on a spatial task in the water maze (Roozendaal 2000).

Interestingly, infusions of a beta-adrenoceptor antagonist 10 min before training into the ipsilateral, and not

the contralateral, BLA blocked the enhancement in an inhibitory avoidance task caused by a GR agonist that was given into the hippocampus immediately after animals were trained. These results support a permissive role of the BLA in modulating GLUC-induced memory consolidation processes involving the hippocampus and suggest that this role is mediated by noradrenergic mechanisms in the BLA.

In recent reviews, McGaugh (2000) emphasized the importance of NE modulation of intra-amygdala processes whereas Kim and Diamond (2002) indicated that the full expression of stress effects on the hippocampus seems to require co-activation of the amygdala and hippocampus, in concert with the direct actions on the hippocampus of neuromodulators, such as corticosterone, 5-hydroxytryptamine, opiates, and corticotropin-releasing factor. Interestingly, we recently found that the bi-phasic modulatory effect of the amygdala on hippocampal LTP depends on both NE and corticosteroids (Akirav and Richter-Levin 2002).

Clearly, more must be learned about the exact mechanisms that mediate amygdala modulation of memory-related processes in the hippocampus. But sufficient evidence exists to conclude that this is at least one of the roles the amygdala has in emotional memory formation.

The Amygdala as a Site for Some Aspects of Emotional Memory

As described above, a vast amount of data support the role of the amygdala in modulating memory-related processing in extra-amygdala brain structures (reviewed by Cahill and McGaugh 1998; McGaugh 2000; Richter-Levin and Akirav 2000; Abe 2001). Furthermore, post-training inactivation or lesioning (McGaugh 2000) of the amygdala has been shown not to impair performance on memory retention for a passive avoidance task, suggesting that the amygdala is not the site for long-term memory of this task. On the other hand, evidence suggests that the amygdala stores information about emotional memories and specifically about fear-producing events (Fanselow and LeDoux 1999; LeDoux 2000; Maren 2001).

A quintessential example of an emotional memory that has been studied extensively is delayed classical conditioning, a phylogenetically early example of simple associative learning. In one of the best studied paradigms—delay conditioning of fear—a neutral conditioned stimulus (CS), such as a tone, is presented just before an electric shock unconditioned stimulus (US). The US is then presented and the two stimuli co-terminate. After pairings, the CS acquires the capacity to elicit responses that typically occur in the presence of danger, such as defensive behavior (freezing), autonomic nervous system responses (changes in blood pressure and heart rate), and neuroendocrine responses (release of hormones from the pituitary and adrenal glands).

Considerable progress has been made in analyzing the neural circuits and mechanisms of learned fear (reviewed by Maren 2001). It is well established today that the amygdala is the hub of this circuitry. The initial

indications were provided by Brown and Schafer (1888), who reported that large lesions of the temporal lobe tamed previously ferocious monkeys. Early in the 20th century, Kluver and Bucy characterized the fairly widespread emotional disturbance caused by such brain damage, and this psychopathology became known as the Kluver-Bucy syndrome. Weiskrantz (1956) reported that many aspects of this syndrome could be produced by damage restricted to the amygdala. Fuster and Uyeda (1971) were the first to show that cells were present within the amygdala that selectively responded to a CS paired with a shock. Subsequently, tract tracking and physiological studies showed that a specific subnucleus within the amygdala, the dorsal lateral nucleus (dLA), was the primary target of pathways that transmitted auditory CS information (Doron and LeDoux 1999), that the LA was a site of CS and US convergence (Romanski and LeDoux 1993), and that associating a tone with a foot-shock induced long-lasting enhancements of the tone-evoked field potentials in the LA (Rogan and others 1997). The above results, together with numerous lesion and pharmacological studies not reviewed here (reviewed by LeDoux 2000; Maren 2001), support the hypothesis that auditory fear conditioning may, in part, be subserved by increases in response of LA neurons to the CS *after* it is paired with the US (but see Garcia and others 1998).

LTP and Learning in the Amygdala: The Case of Fear Conditioning

As mentioned, anatomical and physiological studies have revealed extensive projection to the LA from areas of the auditory thalamus, such as the medial division of the medial geniculate nucleus (MGN) and the posterior intralaminar nucleus. The latter region conveys pain information from the spinal cord, as well as auditory inputs from the inferior colliculus. The LA thus receives convergent CS and US information via its thalamic inputs. Indeed, most of the acoustically responsive cells in the LA are also responsive to noxious somatosensory stimulation, which suggests a possible locus for the information of CS-US associations (LeDoux 2000). The LA may not be the sole site of information convergence. However, the latency of plastic responses measured in LA by field potentials (Rogan and LeDoux 1995; Rogan and others 1997) and single unit responses (Quirk and others 1997) specifically implicate thalamo-amygdala synapses in learning, and synaptic plasticity has been most intensively studied in this pathway.

In vivo studies of amygdala LTP began in 1990, with the demonstration that high-frequency electrical stimulation of the auditory thalamus led to LTP measured in the LA of the anesthetized rat (Clugnet and LeDoux 1990). These studies, along with work done at about the same time in cortico-amygdala pathway in brain slices (Chapman and others 1990), added the amygdala to the still growing list of brain areas amenable to LTP induction. However, the fact that auditory CS information is known to be transmitted along these pathways permitted

a novel series of *in vivo* studies designed to bridge the gap between the artificial methods of LTP induction and learning-induced modification of sensory processing.

In 1995, Rogan and LeDoux, using a small audio speaker placed in the ear canal and a stimulating electrode in the mMGN/posterior intralaminar nucleus, recorded responses in LA neurons to both electrical stimulation and natural acoustic stimuli. The delivery of a high-frequency stimulation to the MGN-LA pathway increased the amplitude of both electrical- and auditory-evoked potentials (Rogan and LeDoux 1995), revealing that the induction of tetanic LTP can enhance the transmission of natural sensory information. The question remained: are these mechanisms used during learning? To determine whether fear conditioning results in learning-related changes in CS processing similar to those caused by LTP induction in auditory CS pathways, Rogan and others (1997) used freely behaving rats to concurrently measure auditory CS-evoked field potentials and CS-evoked fear behavior. Paired presentations of the auditory CS and footshock resulted in an enduring increase in freezing behavior and a parallel potentiation of the CS-evoked potential. Unpaired controls did not show fear conditioning or an increase in auditory evoked potentials (but see Garcia and others 1998). Furthermore, extinction of the conditioned response led to the fall of the CS-evoked response back to baseline levels. These data suggest that fear conditioning results in an increase in the efficacy of LA synapses involved in CS processing.

A complementary study supported the idea that fear conditioning can induce a phenomenon resembling LTP. McKernan and Shinnick-Gallagher (1997) found that EPSCs evoked in LA by electrical stimulation of afferents from the auditory thalamus in brain slices taken from fear-conditioned rats (24 postconditioning) were enhanced compared with the same measures from rats that were not conditioned. Thus, acoustic fear conditioning induced “behavioral LTP” in LA whether synaptic responses were measured “online” in the awake behaving rat or “offline” in amygdala slices obtained from previously conditioned rats.

Most of the *in vivo* work on LTP in the amygdala has focused on the thalamo-amygdala pathway. Yet not all aspects of emotional learning are mediated by low-level thalamic projections to the amygdala. Thalamic inputs are, for example, not capable of mediating associations between complex stimulus representations and their affective attributes, which presumably require cortical inputs to the amygdala (McDonald 1998; LeDoux 2000). Indeed, the amygdala receives inputs from polymodal cortices, including the perirhinal (PRC), entorhinal, and prefrontal cortices (McDonald 1998).

A Gradient of Complexity within the BLA

In addition to expressing fear responses to the cued CS, rats also exhibited these when returned to the chamber in which the tone and the shock were paired, or a chamber in which shocks occur alone. This is called contextual

fear conditioning and, unlike cued conditioning, requires both the amygdala and the hippocampus (see Blanchard and Blanchard 1988; Kim and Fanselow 1992; Phillips and LeDoux 1992). The hippocampus has long been believed to be involved in complex information-processing functions, including spatial, contextual, and relational processing. Damage to areas of the ventral hippocampus (mainly the CA1 and subiculum) interferes with contextual conditioning (Maren 2001). However, in contrast to auditory thalamus and auditory cortex projections, which deliver the acoustic cues to LA (see Romanski and LeDoux 1993), these areas project to the basal (B) (and accessory basal nucleus) (Canteras and Swanson 1992). This raises an interesting possibility, that contextual and auditory fear conditioning may involve different amygdala inputs and circuits.

This conclusion is echoed in our own studies, in which a gradient of plasticity in the BLA (from LA to B) was revealed by comparison of cortical and subcortical stimulation (Yaniv and others 2000). In agreement with this notion, we have recently shown that that burst stimulation of the EC resulted in long-lasting potentiation of the evoked responses in B (Yaniv and others 2003). The EC is often considered the highest-order cortical area in the temporal lobe that receives projections from all the known multimodal association areas as well as from the prefrontal and cingulate cortices. This suggests that in the EC the “specific modality signature of the stimulus must have become highly diluted or transformed into a no longer modality specific but more integrated cognitive signal” (Gloor 1997, pp. 374–5). The EC connections with the amygdala would appear to permit such complex cognitive information to be integrated or associated with emotional (implicit) memory information processed by the amygdala (McDonald 1998) (Fig. 4).

Our hypothesis is further supported by anatomical evidence, showing that in cortico-amygdalar pathways, the heaviest projections to LA originate from unimodal association cortices and are gradually replaced by more complex, polymodal projections when moving toward B (see Gloor 1997; McDonald 1998).

It is interesting to note here that recently late phase LTP, assumed to be indicative of long-term memory capabilities, was demonstrated both in the lateral amygdala (Doyere and others 2003) and in the basal amygdala (Yaniv and others 2003).

A way to validate the “complexity hypothesis” would be to examine to what extent a reversible inactivation of the B, limited to the acquisition phase of conditioning, would result in a selective impairment of contextual conditioning while sparing cued (elemental) conditioning, which would be rather critically dependent on a functional LA. Previous lesion/inactivation studies did not discriminate between the different basolateral amygdala complex (BLA) nuclei, or restricted the type of conditioning to either a cued or a contextual paradigm. Schafe and others (2001) presented evidence indicating LA involvement in cued fear conditioning. However, Desmedt and Jaffard (see Yaniv and others 2003) set out to do the missing experiment, that is, to see whether

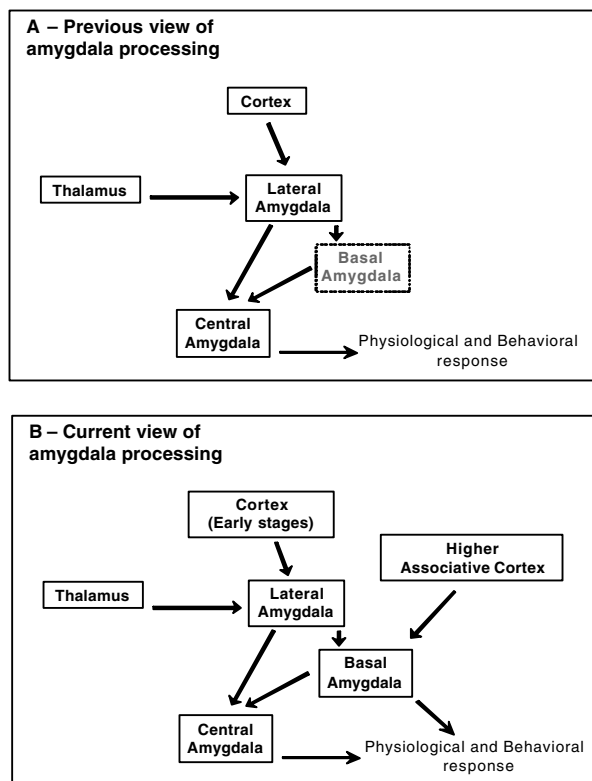


Fig. 4. Previous model of amygdala processing held a simple, linear conception, in which the lateral amygdala is the input and the central amygdala the output sites. Recent findings indicate that a shift should be made toward a parallel processing model in which a gradient of complexity and associativity of incoming information exists from the lateral toward the basal amygdala. Furthermore, the central amygdala is no longer considered the only output nucleus, and the basal amygdala may be responsible for activating a different set of physiological and behavioral responses (for review, see Yaniv and others 2003).

within the BLA it is the B that is involved in contextual fear conditioning. Their results show that Lidocaine injections targeted at the B, prior to acquisition, impaired subsequent freezing to contextual cues but not to the tone CS cue. Although in agreement with previous findings regarding the involvement of the whole basolateral amygdala complex in fear conditioning (Fanselow and LeDoux 1999), their results provide strong evidence for a specific involvement of B in contextual as opposed to cued conditioning.

Biochemical and Molecular Evidence for the Role of the Amygdala in Storing Aspects of Emotional Memory

In addition to electrophysiological findings that support a role for the BLA in long-term emotional memory, biochemical and molecular evidence is accumulating that further strengthens this notion. Schafe and others (2001) demonstrated that the LA is essential for memory consolidation of auditory fear conditioning and that this process is PKA- and protein-synthesis-dependent. Both

late-phase LTP in the amygdala and long-term fear memory were found to require the activation of the extracellular-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) and of cAMP response-element binding protein (CREB). This activation may lead to the synthesis of new proteins and to functional and structural changes believed to underlie long-term memory (Schafe and others 2001). Indeed, the mRNA of several relevant proteins, including alpha-actinin (Ressler and others 2002), Praja 1, neuroligin 1, and E2-uiquitin conjugating factor (Stork and others 2001), was found to increase in the amygdala following the formation of fear memories.

We examined in the rat the activation of ERK2 in the hippocampus and the amygdala following spatial learning under stress. Animals were trained in the water maze in a massed spatial task under high and low stress conditions (cold and warm water, respectively) (Akirav and others 2001). In the dorsal CA1, training was accompanied by increased phosphorylation of ERK2 only in animals that had learned the task (irrespective of the level of stress). In contrast, in the amygdala, significant activation of ERK2 was found only in animals that learned the task well under high levels of stress. The amygdala is not required for either the acquisition or the retention of performance in the water maze task; basolateral amygdala (BLA) lesions did not affect acquisition or retention in a spatial task in the water maze of animals trained at 27°C (Roosendaal and McGaugh 1997). The only animals that did show significant activation of ERK2 in the amygdala were those that had learned the task well under high levels of stress. This finding supports the view that the degree of arousal associated with training determines the degree of the amygdala's participation in the learning. The need for both high stress and learning for the amygdala to be activated is supported by results from fear-conditioning studies. These showed that LTP-like processes in the amygdala occur during fear conditioning but are not induced by the very stressful unconditioned stimulus (US; shock) (McKernan and Shinnick-Gallagher 1997; Rogan and others 1997). In other words, only the interaction of stress and learning components (the fear conditioning) induces long-term associative plasticity in the amygdala.

Two Views of the Amygdala in Emotional Memory Foundation

There are two views regarding the role of the amygdala in emotional memory formation. According to one view, the amygdala modulates memory-related processes in other brain regions, such as the hippocampus. According to the other, the amygdala is a site for some aspects of emotional memory. Here we have presented evidence in support of both views. Indeed, there is no a priori reason to assume that these two views are mutually exclusive. The differential and specific activation of memory-related processes in the amygdala and the hippocampus described above suggests that they may handle different aspects of the same experience. Thus, emotional experi-

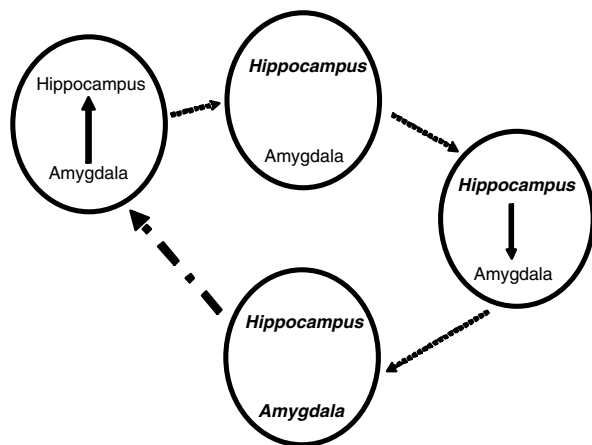


Fig. 5. Dynamic interactions between the amygdala and hippocampus—A substantial body of evidence indicates that during an exposure to an emotional event, the amygdala influences neural plasticity and memory formation processes in the hippocampus. The hippocampus, as well as other projections to the amygdala, may in turn affect neural plasticity in the amygdala. As a result, the specific properties of amygdala-hippocampus interactions may be dependent on previous history of the individual.

ences may lead to parallel activation in emotional (mostly amygdala-based) and nonemotional (mostly hippocampus-based) systems (LeDoux 2000). Activation of the amygdala may in turn modulate memory-related processes in other brain regions, such that the memory traces formed in these regions under emotional conditions that activate also the amygdala will be different from those formed under more neutral conditions.

However, this integrative view of the amygdala's involvement in emotional memory formation intimates another level of complexity; the assumption that emotional conditions induce long-term neural plasticity in the amygdala suggests that following exposure to an emotional experience, the modulation by the amygdala of other brain regions will also be altered. Thus, the interrelations between the amygdala and brain regions, such as the hippocampus, may not be static but dynamic. The way the amygdala will affect memory-related processes in the hippocampus may largely depend on the previous history of the individual (Fig. 5).

References

Abe K. 2001. Modulation of hippocampal long-term potentiation by the amygdala: a synaptic mechanism linking emotion and memory. *Jpn J Pharmacol* 86:18-22.

Abraham WC, Logan B, Greenwood JM, Dragunow M. 2002. Induction and experience-dependent consolidation of stable long-term potentiation lasting months in the hippocampus. *J Neurosci* 22(21):9626-34.

Akirav I, Richter-Levin G. 1999. Biphasic modulation of hippocampal plasticity by behavioral stress and basolateral amygdala stimulation in the rat. *J Neurosci* 1:10530-5.

Akirav I, Richter-Levin G. 2002. Mechanisms of amygdala complex modulation of hippocampal plasticity. *J Neurosci* 22(22):9912-21.

Akirav I, Sandi C, Richter-Levin G. 2001. Differential activation of hippocampus and amygdala following spatial learning under stress. *Eur J Neurosci* 14(4):719-25.

Blanchard DC, Blanchard RJ. 1988. Ethoexperimental approaches to the biology of emotion. *Annu Rev Psychol* 39:43-68.

Bliss TVP, Lomo T. 1973. Long-lasting potentiation of synaptic transmission in the dentate area of an anesthetized rabbit following stimulation of the perforant path. *J Physiol (Lond)* 232:331-56.

Brown S, Schafer A. 1888. An investigation into the functions of the occipital and temporal lobes of the monkey's brain. *Philos Trans R Soc Lond [Biol]* 179:303-27.

Cahill L, McGaugh JL. 1998. Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci* 21:294-9.

Cahill L, Weinberger NM, Roozendaal B, McGaugh JL. 1999. Is the amygdala a locus of "conditioned fear"? Some questions and caveats. *Neuron* 23:227-8.

Canteras NS, Swanson LW. 1992. Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHAL anterograde tract-tracing study in the rat. *J Comp Neurol* 324:180-94.

Chapman PF, Kairiss EW, Keenan CL, Brown TH. 1990. Long-term synaptic potentiation in the amygdala. *Synapse* 6:271-8.

Chiba AA, Kesner RP, Reynolds AM. 1994. Memory for spatial location as a function of temporal lag in rats: role of hippocampus and medial prefrontal cortex. *Behav Neural Biol* 61(2):123-31.

Clugnet MC, LeDoux JE. 1990. Synaptic plasticity in fear conditioning circuits: induction of LTP in the lateral nucleus of the amygdala by stimulation of the medial geniculate body. *J Neurosci* 10:2818-24.

Conrad CD, Lupien SJ, Thanasoulis LC, McEwen BS. 1997. The effects of type I and type II corticosteroid receptor agonists on exploratory behavior and spatial memory in the Y-maze. *Brain Res* 6:76-83.

de Quervain DJ, Roozendaal B, McGaugh JL. 1998. Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature* 20:787-90.

Diamond DM, Bennett MC, Fleshner M, Rose GM. 1992. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus* 2:421-30.

Diamond DM, Dunwiddie TV, Rose GM. 1988. Characteristics of hippocampal primed burst potentiation in vitro and in the awake rat. *J Neurosci* 8:4079-88.

Diamond DM, Fleshner M, Ingersoll N, Rose GM. 1996. Psychological stress impairs spatial working memory: relevance to electrophysiological studies of hippocampal function. *Behav Neurosci* 110:661-72.

Doron NN, LeDoux JE. 1999. Organization of projections to the lateral amygdala from auditory and visual areas of the thalamus in the rat. *J Comp Neurol* 412:383-409.

Doyere V, Schafe GE, Sigurdsson T, LeDoux JE. 2003. Long-term potentiation in freely moving rats reveals asymmetries in thalamic and cortical inputs to the lateral amygdala. *Eur J Neurosci* 17(12):2703-15.

Fanselow MS, LeDoux JE. 1999. Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. *Neuron* 23(2):229-32.

Foy MR, Stanton ME, Levine S, Thompson RF. 1987. Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behav Neural Biol* 48:138-49.

Fuster JM, Uyeda AA. 1971. Reactivity of limbic neurons of the monkey to appetitive and aversive signals. *Electroencephalogr Clin Neurophysiol* 30:291-3.

Garcia R, Paquereau J, Vouimba RM, Jaffard R. 1998. Footshock stress but not contextual fear conditioning induces long-term enhancement of auditory-evoked potentials in the basolateral amygdala of the freely behaving rat. *Eur J Neurosci* 10:457-63.

Gloor P. 1997. The temporal lobe and the limbic system. New York: Oxford University Press.

Kim JJ, Diamond DM. 2002. The stressed hippocampus, synaptic plasticity and lost memories. *Nature Rev Neurosci* 3:453-62.

Kim JJ, Fanselow MS. 1992. Modality-specific retrograde amnesia of fear. *Science* 256:675-7.

LeDoux JE. 2000. Emotion circuits in the brain. *Annu Rev Neurosci* 23:155-84.

- Maren S. 2001. Neurobiology of Pavlovian fear conditioning. *Annu Rev Neurosci* 24:897-931.
- Maroun M, Richter-Levin G. 2003. Exposure to acute stress blocks the induction of long-term potentiation of the amygdala-prefrontal cortex pathway in vivo. *J Neurosci* 23(11):4406-9.
- Matthies H, Frey U, Reymann K, Krug M, Jork R, Schroeder H. 1990. Different mechanisms and multiple stages of LTP. *Adv Exp Med Biol* 268:359-68.
- McDonald AJ. 1998. Cortical pathways to the mammalian amygdala. *Prog Neurobiol* 55:257-332.
- McEwen BS, Sapolsky RM. 1995. Stress and cognitive function. *Curr Opin Neurobiol* 5(2):205-16.
- McGaugh JL. 2000. Memory—a century of consolidation. *Science* 287(5451):248-51.
- McKernan MG, Shinnick-Gallagher P. 1997. Fear conditioning induces a lasting potentiation of synaptic currents in vitro. *Nature* 390:607-11.
- Nguyen PV, Abel T, Kandel ER. 1994. Requirement of a critical period of transcription for induction of a late phase of LTP. *Science* 265:1104-7.
- Oitzl MS, de Kloet ER. 1992. Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. *Behav Neurosci* 106:62-71.
- Packard MG, Cahill L, McGaugh JL. 1994. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proc Natl Acad Sci U S A* 30:8477-81.
- Pavlidis C, Greenstein YJ, Grudman M, Winson J. 1988. Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. *Brain Res* 439:383-7.
- Pavlidis C, Watanabe Y, McEwen BS. 1993. Effects of glucocorticoids on hippocampal long-term potentiation. *Hippocampus* 3:183-92.
- Phillips RG, LeDoux JE. 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav Neurosci* 106:274-85.
- Pikkarainen M, Ronkko S, Savander V, Insausti R, Pitkanen A. 1999. Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the hippocampal formation in rat. *J Comp Neurol* 11:229-60.
- Pugh CR, Tremblay D, Fleshner M, Rudy JW. 1997. A selective role for corticosterone in contextual-fear conditioning. *Behav Neurosci* 111:503-11.
- Quirk GJ, Armony JL, LeDoux JE. 1997. Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. *Neuron* 19:613-24.
- Ressler KJ, Paschall G, Zhou XL, Davis M. 2002. Regulation of synaptic plasticity genes during consolidation of fear conditioning. *Neuroscience* 22(18):7892-902.
- Richter-Levin G, Akirav I. 2000. Amygdala-hippocampus dynamic interaction in relation to memory. *Mol Neurobiol* 22:11-20.
- Richter-Levin G, Akirav I. 2003. Emotional tagging of memory formation—in the search for neural mechanisms. *Brain Res Rev* (in press).
- Rogan MT, LeDoux JE. 1995. LTP is accompanied by commensurate enhancement of auditory-evoked responses in a fear conditioning circuit. *Neuron* 15:127-36.
- Rogan MT, Staubli UV, LeDoux JE. 1997. Fear conditioning induces associative long-term potentiation in the amygdala. *Nature* 390:604-7.
- Romanski LM, LeDoux JE. 1993. Information cascade from primary auditory cortex to the amygdala: corticocortical and corticoamygdaloid projections of temporal cortex in the rat. *Cereb Cortex* 3:515-32.
- Rooszendaal B. 2000. Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology* 25:213-38.
- Rooszendaal B, McGaugh JL. 1997. Basolateral amygdala lesions block the memory-enhancing effect of glucocorticoid administration in the dorsal hippocampus of rats. *Eur J Neurosci* 9:76-83.
- Sandi C, Loscertales M, Guaza C. 1997. Experience-dependent facilitating effect of corticosterone on spatial memory formation in the water maze. *Eur J Neurosci* 9:637-42.
- Schafe GE, Nader K, Blair HT, LeDoux JE. 2001. Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. *Trends Neurosci* 24:540-6.
- Stork O, Stork S, Pape HC, Obata K. 2001. Identification of genes expressed in the amygdala during the formation of fear memory. *Learn Mem* 8(4):209-19.
- Weiskrantz L. 1956. Behavioral changes associated with behavioral ablation of the amygdaloid complex in monkeys. *J Comp Physiol Psychol* 4:381-91.
- Xu L, Holscher C, Anwyl R, Rowan MJ. 1998. Glucocorticoid receptor and protein/RNA synthesis-dependent mechanisms underlie the control of synaptic plasticity by stress. *Proc Natl Acad Sci U S A* 95:3204-8.
- Yaniv D, Schafe GE, LeDoux JE, Richter-Levin G. 2000. A gradient of plasticity in the amygdala revealed by cortical and subcortical stimulation, in vivo. *Neuroscience* 106(3):613-20.
- Yaniv D, Vouimba RM, Diamond DM, Richter-Levin G. 2003. Simultaneous induction of long-term potentiation in the hippocampus and the amygdala by entorhinal cortex activation: mechanistic and temporal profiles. *Neuroscience* 120(4):1125-35.

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