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# The Emotional Brain, Fear, and the Amygdala

**Joseph LeDoux**[1,2]

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**SUMMARY**

1. Considerable progress has been made over the past 20 years in relating specific circuits of the brain to emotional functions. Much of this work has involved studies of Pavlovian or classical fear conditioning, a behavioral procedure that is used to couple meaningless environmental stimuli to emotional (defense) response networks.

2. The major conclusion from studies of fear conditioning is that the amygdala plays critical role in linking external stimuli to defense responses.

3. Before describing research on the role of the amygdala in fear conditioning, though, it will be helpful to briefly examine the historical events that preceded modern research on conditioned fear.

**KEY WORDS:** emotion; amygdala; limbio system; fear.

## THE EMOTIONAL BRAIN IN PERSPECTIVE

In the early part of the twentieth century, researchers identified the hypothalamus as a key structure in the control of the autonomic nervous system (Karplus and Kreidl, 1927). On the basis of these early observations, and their own work (Cannon and Britton, 1925), Cannon and Bard proposed a hypothalamic theory of emotion that consisted of three major points: (1) the hypothalamus *evaluates* the emotional relevance of environmental events; (2) the *expression* of emotional responses is mediated by the discharge of impulses from the hypothalamus to the brainstem; (3) projections from the hypothalamus to the cortex mediate the conscious *experience* of emotion (Bard, 1928; Cannon, 1929). In 1937 Papez added additional anatomical circuits in the forebrain to the theory, but retained the central role of ascending and descending connections of the hypothalamus. The Papez theory, in turn, was extended by MacLean (1949, 1952), who called the forebrain emotional circuits the *visceral brain*, and later, the *limbic system.*

Although the term *limbic system* is still used to refer to the emotional circuits of the brain, the limbic system theory has come under attack on several grounds (see Brodal, 1980; Kotter and Meyer, 1992; LeDoux, 1987, 1991, 1996; Swanson, 1983).

[1] Center for Neural Science, New York University, New York.
[2] To whom correspondence should be addressed at Center for Neural Science, New York University, New York; e-mail: ledoux@cns.nyv.edu



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First, there are no widely accepted criteria for deciding what is and what is not a limbic area. Second, however defined, the limbic system theory does not explain how the brain makes emotions. It points to a broad area of the forebrain located roughly between the neocortex and hypothalamus, but does not account for how specific aspects of any given emotion might be mediated.

The amygdala was part of the MacLean's limbic system theory. However, it did not stand out as an especially important limbic area until 1956 when Weiskrantz showed that the emotional components of the so-called Kluver and Bucy syndrome (Kluver and Bucy, 1937), a constellation of behavioral consequences of temporal lobe damage, were due to the involvement of the of the amygdala. Weiskrantz proposed that amygdala lesions dissociate the affective or reinforcing properties of stimuli from their sensory representations.

## THE AMYGDALA AND FEAR CONDITIONING

In the years following Weiskrantz's publication, a number of studies pursued the role of the amygdala in fear by using a variety of different approaches. However, no consistent conclusions emerged, in large part because complex behavioral tasks that varied considerably from study to study were used. In short, there was little appreciation that different emotional tasks would be mediated by the brain in unique ways. Then, in the late 1970s and early 80s, researchers began using a simple behavioral task, Pavlovian fear conditioning, to study fear networks. This made all the difference.

In Pavlovian fear conditioning, an emotionally neutral conditioned stimulus (CS), usually a tone, is presented in conjunction with an averisve unconditioned stimulus (US), often footshock. After one or several pairings, the CS acquires the capacity to elicit responses that typically occur in the presence of danger, such as defensive behavior (freezing or escape responses), autonomic nervous system responses (changes in blood pressure and heart rate), neuroendocrine responses (release of hormones from the pituitary and adrenal glands), etc. The responses are not learned and are not voluntary. They are innate, species-typical responses to threats and are expressed automatically in the presence of appropriate stimuli. Fear conditioning thus allows new or learned threats to automatically activate evolutionarily tuned was of responding to danger. The ease of establishment, rapidity of learning, long duration of the memory, and stereotyped nature of the responses all speak to the value of the Pavlovian learning as an approach to the study of fear mechanisms and account for the success achieved with this procedure.

Studies from many labs have led to the conclusion that damage to the amygdala interferes with the acquisition and expression of conditioned fear (see LeDoux, 2000; Maren, 2001). Below, I will briefly summarize what is known about how information about danger signals come into the amygdala, how the signals are processed within amygdala, how fear responses are controlled by way of outputs of the amygdala.

Sensory inputs to the amygdala terminate mainly in the lateral nucleus (LA) (see Amaral *et al.*, 1992; LeDoux *et al.*, 1990a; Mascagni *et al.* 1993; McDonald, 1998;

Romanski and LeDoux, 1993; Turner *et al.*, 1980; Turner and Herkenham, 1991), and damage to LA interferes with fear conditioning (Campeau and Davis, 1995b; LeDoux *et al.*, 1990b). Auditory inputs to LA come from both the auditory thalamus and auditory cortex (see LeDoux *et al.*, 1990a; Mascagni *et al.*, 1993; McDonald, 1998; Romanski and LeDoux, 1993), and fear conditioning to a simple auditory CS can be mediated by either of these pathways (Romanski and LeDoux, 1992). It appears that the projection to LA from the auditory cortex is involved with a more complex auditory stimulus pattern (Jarrell *et al.*, 1987), but the exact conditions that require the cortex are poorly understood (Armony *et al.*, 1997). Although some lesion studies have questioned the ability of the thalamic pathway to mediate conditioning (Campeau and Davis, 1995b; Shi and Davis, 1999), single unit recordings show that the cortical pathway conditions slower over trials than the thalamic pathway (Quirk *et al.*, 1995, 1997; Repa *et al.*, 2001), thus indicating that plasticity in the amygdala occurs initially through the thalamic pathway. Recent fMRI studies in humans have found that the human amygdala shows activity changes during conditioning (LaBar *et al.*, 1998; Morris, 1998) and these correlate with activity in the thalamus but not the cortex (Morris *et al.*, 1999).

Animals also exhibit fear responses when returned to the chamber in which the tone and shock were paired, or a chamber in which shocks occur alone. The chamber thus becomes a CS. This is called contextual fear conditioning and requires both the amygdala and hippocampus (see Anagnostaras *et al.*, 2001; Blanchard *et al.*, 1970; Frankland *et al.*, 1997; Kim and Fanselow, 1992; Maren *et al.*, 1997; Phillips and LeDoux, 1992). Areas of the ventral hippocampus (CA1 and subiculum) project to the basal (B) and accesory basal (AB) nuclei of the amygdala (Canteras and Swanson, 1992), which are also known as the basolateral and basomedial nuclei (Pitkanen *et al.*, 1997). Damage to these areas interferes with contextual conditioning (Majidishad *et al.*, 1996; Maren and Fanselow, 1995). Hippocampal projections to B and AB thus seem to be involved in contextual conditioning.

The central nucleus of the amygdala (CE) is the interface with motor systems. Damage to CE interferes with the expression of conditioned fear responses (Gentile *et al.*, 1986; Hitchcock and Davis, 1986; Iwata *et al.*, 1986; Kapp *et al.*, 1979; Van de Kar *et al.*, 1991), while damage to areas that CE projects to selectively interrupts the expression of individual responses. For example, damage to the lateral hypothalamus affects blood pressure but not freezing responses, and damage to the peraqueductal gray interferes with freezing but not blood pressure responses (LeDoux *et al.*, 1988). Similalry, damage to the bed nucleus of the stria terminalis has no effect on either blood pressure or freezing responses (LeDoux *et al.*, 1988) but disrupts the conditioned release of pituitary-adrenal stress hormones (Van de Kar *et al.*, 1991). Because CE receives inputs from LA, B, and AB (Pitkanen *et al.*, 1997), it is in a position to mediate the expression of conditioned fear responses elicited by both acoustic and contextual CSs.

The direct projection from LA to CE seems to be sufficient for conditioning to an auditory CS, since lesions of B and AB have no effect on fear conditioning to a tone (Majidishad *et al.*, 1996). The exact manner in which LA and CE communicate is not clear (Royer *et al.*, 1999), but the intercalated cell mass located between LA and CE may be involved (Royer *et al.*, 1999).

## CELLULAR AND MOLECULAR MECHANSIMS UNDERLYING FEAR CONDITIONING

With key elements of the circuitry identified, researchers have turned to questions about the cellular and molecular basis of fear conditioning.

Cells in LA are responsive to nociceptive stimulation, and some of the same cells respond to auditory inputs as well (Romanski *et al.*, 1993). Thus, the substrate for conditioning (convergence of CS and US information) exists in LA. Indeed, during fear conditioning the firing properties of cells in LA are modified (Collins and Pare, 2000; Maren, 2000; Quirk *et al.*, 1995, 1997; Repa *et al.*, 2001). Conditioned plasticity also occurs in the auditory cortex (Quirk *et al.*, 1997; Weinberger, 1995, 1998). However, the response latencies in LA within trials (<20 ms) and the rate of acquisition (1–3 trials) is best explained in terms of direct auditory thalamo-amygdala transmission, rather than cortico-amygdala transmission, since conditioned responses in the auditory cortex occur later both within trials and across trials (Quirk *et al.*, 1997). Plasticity in the auditory thalamus (Weinberger, 1995, 1998) could contribute to LA plasticity. Plasticity has also been observed in B (Maren *et al.*, 1991; Uwano *et al.*, 1995) and CE (Pascoe and Kapp, 1985) during aversive conditioning, but the acoustic responses latencies both before and after conditioning are longer than in LA. LA thus seems to be both the initial point of sensory processing and the initial site of plasticity in the amygdala.

Plasticity in the amygdala has also been studied using long-term potentiation (LTP), a physiological procedure pioneered in studies of the hippocampus (Bliss and Lomo, 1973). LTP is believed to engage the cellular mechanisms similar to those that underlie natural learning (e.g., Bliss and Collingridge, 1993; Lynch, 1986; Malenka and Nicol1 1999; Martin *et al.*, 2000; Nicoll and Malenka, 1995). However, it has been difficult to specifically relate LTP to memory in the hippocampus (see Barnes, 1995; Eichenbaum, 1997; Martin *et al.*, 2000; Stevens, 1998).

Considerable success has been achieved in the attempt to relate LTP memory in studies of the amygdala. This is due to the fact that specific synapses (those that transmit the CS to the LA) have been implicated in a specific form of memory involving the amygdala, namely fear conditioning. Studies using extracellular recordings in vivo of field potentials in LA have shown that LTP occurs in fear processing pathways, that the processing of natural stimuli similar to those used as a CS in conditioning studies is facilitated following LTP induction, and that fear conditioning and LTP induction produce similar changes in the processing of a CS (Clugnet and LeDoux, 1990; Rogan and LeDoux, 1995; Rogan *et al.*, 1997). While exploration of mechanisms are difficult in these in vivo studies, they nevertheless provide some of the strongest evidence to date in any brain system of a relation between natural learning and LTP (Barnes, 1995; Eichenbaum, 1995; Stevens, 1998). LTP has also been found in vivo in the hippocampal-amygdala pathway, which is believed to be involved in context conditioning (Maren and Fanselow, 1995).

The most extensively studied form of LTP occurs in the CA1 region of the hippocampus and involves the interaction between presynaptic glutamate and two classes of postsynaptic receptors (Nicoll and Malenka, 1995). First, glutamate binds to AMPA receptors and depolarizes the postsynaptic cell. The depolarization removes

the magnesium block on the NMDA class of receptors. Calcium then flows into the cell through the NMDA channel and voltage-gated calcium channels (see Cavus and Teyler, 1996; Magee and Johnston, 1997; Tang *et al.*, 1999) and and triggers a host of intracellular events that ultimately result in gene induction and synthesis of new proteins (see Dudai, 1989; Huang *et al.*, 1996; Shaywitz and Greenberg, 1999; Silva *et al.*, 1998). These then help stablize the changes over long periods of time.

There have been a number of in vitro studies of LTP in the amygdala, mostly involving pathways carrying information from the thalamus or cortex to LA and B (Bauer *et al.*, 2002; Chapman *et al.*, 1990; Chapman and Bellavance, 1992; Gean *et al.*, 1993; Huang *et al.*, 1996; Huang and Kandel, 1998; Weisskopf *et al.*, 1999). Recent studies indicate that as in the CA1 region of hippocampus LTP in the thalamo-amygdala pathway requires an elevation of postsynaptic calcium, and that the calcium can enter through either NMDA receptors or voltage-gated calcium channels (VGCCs), depending on the manner in which LTP is induced (Bauer *et al.*, 2002; Weisskopf *et al.*, 1999).

Behavioral studies have shown that blockade of NMDA receptors in the LA/B region prevents fear conditioning (Fendt, 2001; Gewirtz and Davis, 1997; Lee and Kim, 1998; Maren and Fanselow, 1996; Miserendino *et al.*, 1990; Rodrigues *et al.*, 2002). Recently, it has also been shown that disruption of VGCCs in LA/B disrupts fear conditioning. These studies suggest that during fear conditioning, both the NMDA- and VGCC-dependent forms of LTP occur in the amygdala (Bauer *et al.*, 2002; Blair *et al.*, 2001; Schafe *et al.*, 2001).

It is generally believed that long-term retention of the effects of learning involve intracellular cascades that are triggered by the influx of calcium during postsynaptic depolarization (see Dudai, 1989; Kandel, 1997; Schafe *et al.*, 2001; Silva *et al.*, 1998; Sweatt, 2001). The rise in calcium then triggers several kinases and transcription factors, including CAM Kinase II, MAP kinase, cAMP-dependent kinase (PKA), protein kinase C, and cAMP response element binding protein (CREB). These act, possibly in concert, to induce genes and initiate synthesis of new proteins. While these mechanisms have been worked out in best in reduced preparations, such as studies of invertebrates or studies of LTP (see Huang *et al.*, 1996; Kandel, 1999; Yin *et al.*, 1994), many of these same intracellular signals have been implicated in fear conditioning through studies of genetically altered mice (Abel *et al.*, 1997; Bourtchouladze *et al.*, 1994; Mayford *et al.*, 1996) or by infusing of agents that affect the pathways in the brain (Atkins *et al.*, 1998; Bourtchouladze *et al.*, 1998; Josselyn *et al.*, 1998; Schafe *et al.*, 1999, 2000).

## MEMORY VS. MODULATION

In spite of a wealth of data implicating the amygdala in fear conditioning, some authors have recently suggested that the amygdala is not a site of plasticity or storage during fear conditioning (e.g., Cahill and McGaugh, 1998; Vazdarjanova and McGaugh, 1998). They argue instead that the amygdala modulates memories that are formed elsewhere. It is clear that there are multiple memory systems in the brain (see Eichenbaum, 1994; McDonald and White, 1993; Squire *et al.*, 1993), and that the

amygdala does indeed modulate memories formed in other systems, such as declarative or explicit memories formed through hippocampal circuits or habit memories formed through striatal circuits (Packard *et al.*, 1994). However, evidence for a role of the amygdala in modulation should not be confused with evidence against a role in plasticity. That the amygdala is indeed important for learning is suggested by studies showing that inactivation of the amygdala during learning prevents learning from taking place (e.g., Helmstetter and Bellgowan, 1994; Muller *et al.*, 1997). Further, if the inactivation occurs immediately after training, then there is no effect on subsequent memory (Wilensky *et al.*, 1999), showing that the effects of pretraining treatment is on learning and not on processes that occur after learning. The amygdala thus seems to be essential for fear learning, and does not modulate its own learning.

## FEAR CONDITIONING AND THE HUMAN AMYGDALA

Damage to the amygdala (Bechara *et al.*, 1995) or areas of temporal lobe including the amygdala (LaBar *et al.*, 1995) produces deficits in fear conditioning in humans. Further, fear conditioning leads to increases in amygdala functional activity, as measured by fMRI (Buchel *et al.*, 1998; LaBar *et al.*, 1998), and these effects also occur to subliminal stimuli (Morris *et al.*, 1998). Additionally, when the activity of the amygdala during fear conditioning is cross-correlated with the activity in other regions of the brain, the strongest relations are seen with subcortical (thalamic and collicular) rather than cortical areas, further emphasizing the importance of the direct thalamao-amgdala pathway in the human brain (Morris *et al.*, 1999). Other aspects of emotion and the human brain area are reviewed in Phelps and Anderson (1997) and Irwin and Davidson and Irwin (1999).

## CONSCIOUS FEAR

Fear and fear learning have been dealt with here without addressing the conscious experience of fear that occurs when humans are in danger. While this is more a problem about consciousness than about emotion, it is an important problem that research on emotion may be able to contribute to.

We are far from solving what consciousness is, but a number of theorists (Johnson-Laird, 1993; Kihlstrom, 1987; Kosslyn and Koenig, 1992) have proposed that it may be related to working memory (Baddley, 1998), a serially organized mental workspace where things can be compared and contrasted and mentally manipulated. A variety of studies of humans and nonhuman primates point to the prefrontal cortex, especially the dorsolateral prefrontal areas—as well as the anterior cingulate and orbital cortical regions—as being involved in working memory (Braver *et al.*, 1997; Carter *et al.*, 1998; Fuster, 1998; Goldman-Rakic, 1996). Immediately present stimuli and stored representations are integrated in working memory by way of interactions between prefrontal areas, sensory processing systems (which serve as short-term memory buffers), and the long-term explicit (declarative) memory system involving

the hippocampus and related areas of the temporal lobe. In the case of an affectively charged stimulus, such as a trigger of fear, the same sorts of processes will be called upon as for stimuli without emotional implications, but in addition, working memory will become aware of the fact that the fear system of the brain has been activated. This additional information, when added to perceptual and mnemonic information about the object or event, could be the condition for the subjective experience of an emotional state of fear (LeDoux, 1996).

By way of projections to cortical areas the amygdala can influence the operation of perceptual and short-term memory processes, as well as processes in higher order areas. Although the amygdala does not have extensive connections with the dorsolateral prefrontal cortex, it does communicate with the anterior cingulate and orbital cortex, two other components of the working memory network. But in addition, the amygdala projects to nonspecific systems involved in the regulation of cortical arousal and controls bodily responses (behavioral, autonomic, endocrine), which then provide feedback that can influence cortical processing indirectly. Thus, working memory receives a greater number of inputs, and receives inputs of a greater variety, in the presence of an emotional stimulus than in the presence of other stimuli. These extra inputs may just be what is required to add affective charge to working memory representations, and thus to turn subjective experiences into emotional experiences.

## THE EMOTIONAL BRAIN IN LIGHT OF CONDITIONED FEAR

Although the particulars have changed, the general view of how threatening stimuli incite animals to defend themselves remains somewhat the same since the early proposals by Cannon and Papez. For example, both Cannon and Papez proposed that sensory stimuli leaving the thalamus travel to the subcortical "emotional" processing regions as well as to neocortical sensory processing regions, which in turn send information to the same subcortical emotional regions. And for both Papez and Cannon, the hypothalamus was the key subcortical region involved in emotional processing. Its job was to send signals to the brainstem, so that emotions could be expressed as bodily responses, and to the cortex, so that emotions could be experienced as subjective states.

Contemporary research largely agrees with this general picture, painted largely on the basis of anatomcial speculation in the 1920s and 30s. However, with the accumulation of a great deal of empirical research, the amygdala has replaced the hypothalamus as the centerpiece of the subcortical networks involved in detecting and responding to threats. Thus, projections from the amygdala to the brainstem are involved in the expression of fear responses, and projections from the amygdala to the cortex are believed to contribute to the experience of fear and other cognitive aspects of emotional processing.

Still, it would be wrong to conclude that the field has not advanced since the early days. Clearly, we now know much more about how the fear system works. In addition to pinpointing the amygdala as a key structure in the processing of danger, much has been learned about how the amygdala accomplishes its job. The anatomical inputs to and outputs from the amygdala are understood in exquisite detail, as are

the internal connections that mediate processing within the amygdala. Further, the nature of physiological encoding of fear situations by neurons within the amygdala is beginning to be understood as well.

I have focused on the neural basis of fear conditioning in this chapter. Other models of emotional processing implicating the amygdala and other brain regions have been studied as well (e.g., Everitt *et al.*, 1999; Rolls, 1999). While much less is known about the detailed organization of emotions other than fear, this is an important area for future work.

We are poised to now understand the neural basis of at least a simple form of fear processing, and this will surely lay a foundation for further explorations of the neural basis of fear and fear disorders, and perhaps other emotions as well.

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