EMOTION: Clues from the Brain

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INTRODUCTION

Despite the obvious importance of emotion to human existence, scientists concerned with human nature have not been able to reach a consensus about what emotion is and what place emotion should have in a theory of mind and behavior. Controversy abounds over the definition of emotion, the number of emotions that exist, whether some emotions are more basic than others, the commonality of certain emotional response patterns across cultures and across species, whether different emotions have different physiological signatures, the extent to which emotional responses contribute to emotional experiences,

the role of nature and nurture in emotion, the influence of emotion on cognitive processes, the dependence of emotion on cognition, the importance of conscious versus unconscious processes in emotion, and on and on (see Ekman & Davidson 1994).

Although there has been no shortage of psychological research on these topics, the findings have not resolved many of the issues in a compelling manner. But psychological research is not the only source of information about the nature of emotion. Information about the representation of emotion in the brain may shed light on the nature of emotional processes. First, information about how emotion is represented in the brain can provide constraints that could help us choose between alternative hypotheses about the nature of some emotional process. Second, findings about the neural basis of emotion might also suggest new insights into the functional organization of emotion that were not apparent from psychological findings alone. The brain, in other words, can constrain and inform our ideas about the nature of emotion.

This review examines the neural basis of emotion and considers how research on brain mechanisms can potentially help us to understand emotion as a psychological process.

NEURAL BASIS OF EMOTION

Studies of the neural basis of emotion have a long history within neuroscience (see LeDoux 1987, 1991). This research culminated around mid-century in the limbic system theory of emotion (MacLean 1949, 1952), which claimed to have identified the limbic system as the mediator of emotion. However, in recent years both the limbic system concept (Brodal 1982, Swanson 1983, Kotter & Meyer 1992) and the limbic system theory of emotion (Le-Doux 1991) have been questioned. Despite problems with the conceptualization of the brain system that mediates emotion in general, there has been a great deal of systematic and productive research on the neural basis of specific emotions. It is not known whether there is a general purpose system of emotion in the brain, but if there is it will be identified readily by synthesizing across studies of specific emotions. This review focuses on the neural basis of fear, an emotion that has been studied extensively at the neural level.

Neural Basis of Fear

Fear is an especially good emotion to use as a model. It is a common part of life, almost from the beginning. The expression of fear is conserved to a large extent across human cultures and at least to some extent across human and nonhuman mammalian species, and possibly across other vertebrates as well. There are well-defined experimental procedures for eliciting and measuring

fear, and many of these can be used in more or less identical ways in humans and experimental animals. Further, disorders of fear regulation are at the heart of many psychopathologic conditions, including anxiety, panic, phobic, and posttraumatic stress disorders. It would be an important achievement if, by focusing on fear, we were able to generate an adequate theory of fear, even if it applied to no other emotion.

The following survey of the neural basis of fear concentrates on studies of fear conditioning. This approach has been particularly successful in identifying the neural system that mediates learned fear and in uncovering some of the cellular mechanisms that might be involved.

Fear conditioning is a form of Pavlovian (classical) conditioning. Pavlov is best remembered for his studies of alimentary conditioning, in which he elicited salivation in dogs by presenting stimuli that had been associated with the delivery of food (Pavlov 1927). He also determined that animals will exhibit conditioned reflexes that allow them to protect themselves against harmful stimuli by responding to warning signals. Pavlov referred to the latter as defense conditioning. Today, Pavlovian defense conditioning is usually referred to as fear conditioning (Brown et al 1951, Kamin 1965, McAllister & McAllister 1971, Millenson & de Villiers 1972, Bouton & Bolles 1980, Davis 1992, Kapp et at 1992, Fanselow 1980, LeDoux 1993a).

In a typical fear conditioning experiment, the subject is exposed to a tone or light (the conditioned stimulus, CS) that is followed by a brief shock (the unconditioned stimulus, US; see Figure 1). Conditioning occurs after only a few pairings (one pairing is enough if the US is sufficiently intense) (Fanselow & Bolles 1979). The effects of conditioning can be assessed directly by measuring defense responses elicited by the CS, including freezing responses (Blanchard & Blanchard 1972, Bouton & Bolles 1980, Fanselow 1980, LeDoux et al 1984) or changes in autonomic (Smith et al 1980, Cohen & Randall 1984, LeDoux et al 1984) and endocrine (Mason 1968, van de Kar et al 1991) activity. These are hard-wired or innate reactions to threat that come to be coupled to the CS through the conditioning process. The effects of fear conditioning can also be assessed indirectly by measuring the potentiation of reflexes, such as the eyeblink or startle reflex (e.g. Brown et al 1951, Davis et al 1987, Weisz et al 1992), in the presence of the CS, by measuring the inhibition of pain by the CS (e.g. Watkins & Mayer 1982, Fanselow & Helmstetter 1988), or by measuring the degree to which the animal's ongoing behavior is interfered with or suppressed by the CS (e.g. Estes & Skinner 1941, Hunt & Brady 1955, Bouton & Bolles 1980, Leaf & Muller 1965).

Neural Pathways Mediating Fear Conditioning

The logic underlying the search for the neural pathways in fear conditioning is straightforward. Conditioning is believed to involve the intersection in the

brain of pathways transmitting information about the CS and the US (Pavlov 1927, Konorski 1967, Hebb 1949). Because the US must intersect a variety of CS pathways originating in different sensory systems, it seems that the crucial changes that underlie conditioning should involve modifications in the network that is involved in the processing of the specific CS used. Thus, if one were able to follow the processing of the CS through its sensory system and beyond to the motor system controlling the conditioned responses (CRs), the circuitry within which conditioning occurs would presumably be known.

How, then, should one attempt to follow the processing of the CS? The strategy that has worked best uses the classical lesion method in conjunction with modern neuroanatomical tracing techniques. For example, if the CS is an acoustic stimulus, then the CS pathway must begin in the auditory system and should continue as an efferent projection out of the auditory system. Since the auditory system is a linearly organized system involving relays from lower to higher centers, it is possible to determine, with the lesion method, whether the auditory CS has to rise through the entire pathway for conditioning to occur. By using neuroanatomical tracing techniques it is then possible to examine the connections of the highest auditory station required and, thereby, define the
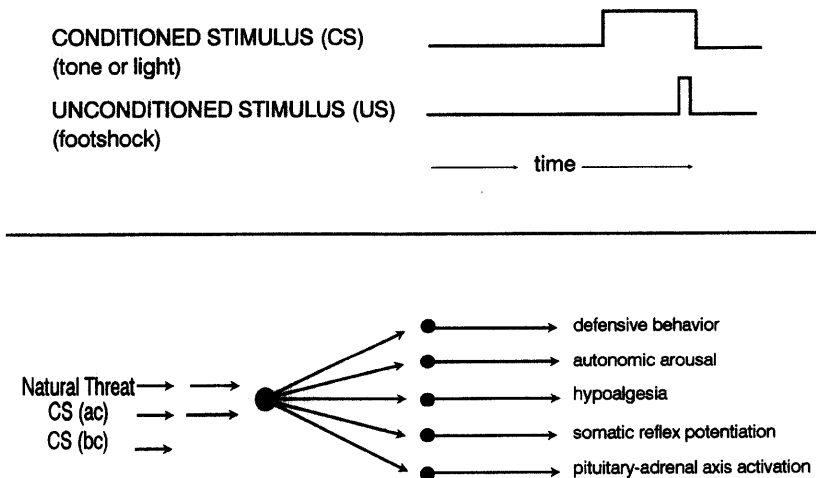
Figure 1 Fear conditioning involves the temporal association of an innocuous conditioned stimulus (CS), such as a light or tone, with a noxious unconditioned stimulus (US), such as footshock. After conditioning (ac), but not before conditioning (bc), the CS acquires the capacity to activate a variety of brain systems involved in the control of defensive responses. These same responses are elicited by natural or unlearned threatening stimuli. Fear conditioning is stimulus learning, not response learning, and it allows new stimuli to gain control over hard-wired, evolutionarily perfected, defensive response control networks.

next possible links in the pathway, which can each in turn be lesioned to determine which one constitutes the key link.

Research in the early 1980s showed that lesions of the midbrain and thalamic stations of the auditory pathway prevented conditioning but that lesions of the auditory cortex had no effect (LeDoux et al 1984). This suggested that the CS must exit the auditory system at the level of the thalamus. Anatomical tracing techniques were then used to show that the auditory thalamus projects not only to the auditory cortex but also to the amygdala (LeDoux et al 1985). Additional studies showed that interruption of the connections between the auditory thalamus and the amygdala interferes with conditioning (LeDoux et al 1986, Iwata et al 1986) and that the lateral nucleus of the amygdala is the crucial region for the reception of the auditory stimulus (LeDoux et al 1990a,b; Clugnet et al 1990).

Although the auditory cortex is not necessary for conditioning, projections from the auditory thalamus through the auditory cortex and to the amygdala (Romanski & LeDoux 1993a,b) are sufficient to mediate simple acoustic fear conditioning (conditioning with a single auditory CS paired with the US) (Romanski & LeDoux 1992). This suggests that the thalamo-amygdala and thalamo-cortico-amygdala pathways are equipotential in mediating simple conditioning (Romanski & LeDoux 1992). However, auditory cortical areas, and presumably cortico-amygdala connections, are required for differential conditioning (in which two auditory stimuli are presented, one paired with the US and the other not) (Jarrell et al 1987).

The direct thalamic pathway to the amygdala is shorter and thus faster, but its capacity to represent the auditory stimulus is more limited (Bordi & LeDoux 1994a,b). The thalamo-cortico-amygdala pathway, which involves several cortico-cortical links before reaching the amygdala (Romanski & LeDoux 1993a,b), is longer and slower, but its capacity to represent the auditory stimulus is considerably greater. The thalamic pathway is sufficient for the rapid triggering of emotion by simple stimulus features (as in simple conditioning), whereas the cortical pathway appears to be needed for emotional reactions coupled to perceptually complex stimulus objects (as in differential conditioning). Within the amygdala, the quick-and-dirty thalamic inputs and the slower but more accurate cortical inputs converge in the lateral nucleus (LeDoux et al 1991). The lateral nucleus is the sensory interface of the amygdala and possibly a crucial site of integration of information from parallel auditory projections during fear conditioning (LeDoux et al 1990b, LeDoux 1992).

Whenever a CS is paired with a US, some conditioning accrues to the background or to contextual stimuli that are also present in the environment (e.g. Rescorla & Wagner 1972). Recent studies have shown that contextual conditioning, like conditioning to a CS, is dependent on the amygdala, but

unlike CS conditioning, it is also dependent upon the hippocampus (Phillips & LeDoux 1992b, Kim & Fanselow 1992, Selden et al 1991). Although the exact direction of information flow between these structures is not known, the hippocampus (by way of the subiculum) projects to the lateral nucleus (and several other amygdala nuclei) (Ottersen 1982, Phillips & LeDoux 1992a). As a result, the hippocampus, long believed to be involved in complex information processing functions, including spatial, contextual, and relational processing (O'Keefe & Nadel 1978, Eichenbaum 1992, McNaughton & Barnes 1990, Nadel & Willner 1980, Rudy & Sutherland 1992), may be a kind of higher-order sensory structure in fear conditioning. That is, the hippocampus may relay environmental inputs pertaining to the conditioning context to the amygdala, where emotional meaning is added to context just as it is added to thalamic or cortical sensory information. Once learned, this kind of contextual fear conditioning might allow the organism to distinguish between those situations in which it is appropriate to defend oneself against a stimulus vs situations in which it is not necessary (e.g. a bear in the woods vs in the zoo).

Just as the lateral nucleus is the input system of the amygdala, the central nucleus is the output system (LeDoux 1993a, Davis 1992, Kapp et al 1984, 1990). Lesions of the central nucleus interfere with the expression of conditioned responses expressed through a variety of motor modalities, including freezing behavior, sympathetic and parasympathetic autonomic responses, neuroendocrine responses, the potentiation of startle and eyeblink reflexes, and the suppression of pain. Most interestingly, lesions of areas to which the central nucleus projects interfere separately with individual responses. For example, projections to the central gray are involved in freezing responses (Iwata et al 1987, LeDoux et al 1988, Wilson & Kapp 1994); projections to the lateral hypothalamus are involved in sympathetic autonomic responses (Smith et al 1980, Iwata et al 1987, LeDoux et al 1988); projections to the bed nucleus of the stria terminalis are involved in neuroendocrine responses (van de Kar et al 1991); and projections to the nucleus reticularis caudalis pontis are involved in the potentiation of startle responses (Rosen et al 1991).

The amygdala is involved in both the acquisition and the expression of fear conditioning (e.g. LeDoux 1987, 1990, 1992; Davis et al 1987; Davis 1992; Kapp et al 1984, 1990, 1992; Gentile et al 1986). Even with extensive over-training, posttraining lesions of the amygdala interfere with fear conditioning (Kim & Davis 1993).

Although much of the work on fear conditioning has used auditory CSs, some studies have used visual stimuli (e.g. Davis et al 1987; Davis 1992; LeDoux et al 1989). In general, the circuitry involved appears to be quite similar. However, because the visual connections with the amygdala in the rat are poorly understood, the input circuitry is not as clear as it is for auditory conditioning.

In summary, the neural pathways through which defense responses are conditioned and expressed to auditory stimuli have been well defined (see Figure 2). The amygdala appears to play a central role in this circuitry. It is located between the sensory system that processes the CS and the motor systems that control the conditioned responses. Although some learning may occur in the sensory and motor systems (see below), important aspects of fear conditioning probably occur in the amygdala because it is the only part of the
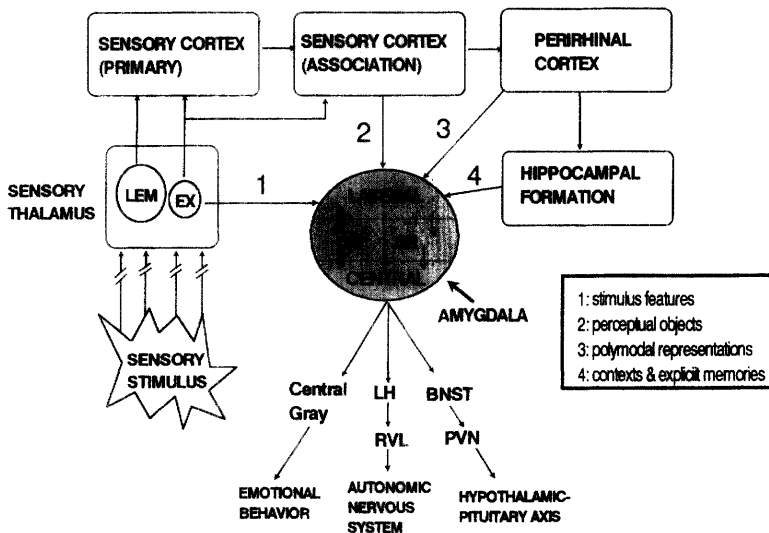

Figure 2   Neural circuits of fear conditioning. The neural pathways by which a sensory CS elicits emotional responses involve the relay of sensory inputs to the thalamus. While the lemniscal nuclei (LEM) transmit only to the primary sensory cortex, the extralemniscal areas (EX) transmit to primary sensory and association regions of the cortex, as well as to the lateral nucleus of the amygdala. This region of the amygdala also receives inputs from sensory association areas of the neocortex, as well as from polymodal areas such as the perirhinal cortex and the hippocampal formation. The thalamo-amygdala sensory projection (1) has been implicated in simple fear conditioning [one conditioned stimulus (CS) paired with an unconditioned stimulus (US)]; the cortico-amygdala sensory projection (2) in differential fear conditioning (one CS paired with US, another not paired); and the hippocampo-amygdala projection (4) in contextual conditioning (conditioning to situational cues other than the CS). The hippocampal projection may also be involved in conditioning of fear to explicit or declarative memories that occur in the presence of an US, but this has not been studied. The role of the perirhinal projection to amygdala (3) is not known, but it may have something to do with the elicitation of fear by complex polymodal stimulus representations. The central nucleus of the amygdala is the interface with motor systems, as it connects with various brainstem areas involved in the regulation of specific defense response networks. Projections to the central gray control freezing and other defensive behaviors; projections to the lateral hypothalamus (LH) and from there to the rostral ventral lateral medulla (RVL) control sympathetic autonomic nervous system responses; and projections to the bed nucleus of the stria terminalis (BNST) and paraventricular hypothalamus control stress reactions involving the pituitary-adrenal axis. The amygdala nuclei are the sensory- and motor-independent parts of the circuitry and are likely to play important integrative roles in fear conditioning.

circuitry that is involved independent of the CS and CR modalities. Studies of cellular mechanisms have thus focused on the amygdala.

Cellular Mechanisms Involved in Fear Conditioning

A main reason for wanting to understand the neural circuit underlying conditioning is that such information isolates from the vast numbers of neurons and their connections the particular neurons and connections that must be modified during learning and within which the changes might be stored either temporarily or permanently. The neural systems level of analysis thus guides the cellular level analysis, and findings at the cellular level reveal mechanisms about how the brain actually works. Although the search for the cellular basis of fear conditioning is in its infancy, important discoveries have begun to shed light on the underlying mechanisms.

CS-US CONVERGENCE   The neural basis of classical conditioning involves convergence of the CS and US pathways in the brain (Pavlov 1927, Hebb 1949, Konorski 1967). If, as the systems level of analysis suggests, the amygdala is a crucial site of conditioning, then cells in the amygdala should respond to both the CS and the US. Recent studies have mapped the responses of amygdala neurons to auditory stimuli similar to those used in conditioning experiments (Bordi et al 1992, 1993; Romanski et al 1993). This work has shown that neurons in the lateral nucleus of the amygdala are particularly responsive to auditory CS-like stimulation. Responses in other areas tend to be weaker and to have longer latencies. This reinforces the conclusion that the lateral nucleus is the sensory interface of the amygdala. Romanski et al (1993) found that essentially every cell that responded to auditory stimuli also responded to noxious somatosensory stimulation similar to that used as a US. The lateral nucleus of the amygdala is thus a site of CS-US convergence and may be a crucial site of the cellular changes that underlie learning. However, one of the key missing pieces of information about the neural basis of fear conditioning is the origin of the US inputs to the amygdala.

PHYSIOLOGICAL PLASTICITY INDUCED BY CS-US PAIRING   Neurons in a number of brain regions undergo physiological changes during aversive classical conditioning (see Thompson et al 1983). This fact discourages the use of unit recording techniques to find the critical locus of learning. An alternative strategy is to first identify the essential neural circuit underlying a particular learned response through lesion studies and then examine the plastic properties of the neurons in the circuit. These are the neurons that are most likely to undergo changes in physiological responsivity that are essential to the learning task.

With key aspects of the fear learning circuitry now identified (see above), it is useful to consider the extent of physiological plasticity that has been ob-

served in these areas. Studies of the physiology of learning have suggested that many brain regions exhibit physiological changes during learning. Thus, it is perhaps not surprising that plasticity has been found throughout the fear conditioning circuitry: in the auditory thalamic areas that project to the amygdala (Gabriel et al 1976, Ryugo & Weinberger 1978, Edeline & Weinberger 1992); in the auditory cortex (Weinberger & Diamond 1987, Edeline & Weinberger 1993); in the lateral, basolateral, and central nuclei of the amygdala (LeGal LaSalle & Ben-Ari 1981, Muramoto et al 1993, Pascoe & Kapp 1985); and in the lateral hypothalamus (Ono et al 1988). This ubiquitous plasticity in the conditioning circuitry would be trivial if plasticity in all levels of the pathway reflects learning by some early station (such as the auditory thalamus). On the other hand, it would be significant if it means that each link in the pathway is plastic and that plasticity in different locations serves different functions. Plasticity in the sensory structures could make stimulus processing more efficient; plasticity in motor systems could make the execution of the responses more efficient; and plasticity in the amygdala could represent the integrative (stimulus- and response-independent) aspects of learning.

LTP AND THE AMYGDALA   Learning at the cellular level is generally believed to involve changes in synaptic transmission (Hebb 1949, Kandel & Spencer 1968, Squire 1987). A great deal of work has thus sought to identify the mechanisms by which experience modifies the efficiency of synaptic transmission. Most of this work has involved long-term potentiation (LTP). In an LTP experiment, a pathway is stimulated at a high frequency, and as a result, the response to a low-frequency test stimulus is amplified. LTP has been studied most extensively in the hippocampus (Lynch 1986, Cotman et al 1988, Brown et al 1988, Malenka & Nicoll 1993, Madison et al 1991, Bliss & Collingridge 1993) but has also been demonstrated in other brain regions, including the lateral and basal nuclei of the amygdala (Clugnet & LeDoux 1990, Chapman et al 1990).

Several properties of LTP make it attractive as a memory mechanism (Lynch 1986, Brown et al 1988). LTP is experience dependent and synapse specific: Cells receive many inputs, but the response is only amplified for those inputs that were stimulated. LTP exhibits cooperativity: The induction of LTP depends on the simultaneous activation of many afferents. LTP exhibits associativity: It can be produced by simultaneous stimulation of two pathways using stimuli that are not effective individually. LTP is stable and long lasting. Although the relationship between LTP and behavioral learning and memory is still unclear and controversial (Teyler & DiScenna 1987, Morris 1992, McNaughton & Barnes 1990, O'Keefe 1993), an LTP-like phenomenon might underlie some aspects of learning, including fear conditioning mediated by the amygdala.

PHARMACOLOGICAL SIMILARITY OF LTP AND FEAR CONDITIONING   One way to link LTP to learning and memory is to determine whether similar pharmacological manipulations are involved (Lynch et al 1991, Staubli 1994). The pharmacology of the classic form of LTP has been well characterized (e.g. Lynch et al 1991, Madison et al 1991, Malenka & Nicoll 1993). It involves the binding of the excitatory amino acid transmitter, L-glutamate, to two classes of postsynaptic excitatory amino acid receptors, NMDA and non-NMDA receptors. The NMDA receptor channel is normally opened only when the cell membrane is depolarized by the prior binding of Glu to non-NMDA receptors. The opening of the NMDA channel is a crucial step in LTP. LTP does not occur if the channel is blocked by an antagonist. In contrast, the expression of established LTP is not affected by NMDA blockade.

In 1949 Hebb postulated that learning at the cellular level involved the simultaneous activity of pre- and postsynaptic neurons. That is, if the postsynaptic neuron is depolarized when the presynaptic input arrives, the connection will be strengthened. The NMDA receptor appears to be a neural instantiation of the Hebb rule. It requires that presynaptically released Glu bind to postsynaptic NMDA receptors while the postsyanptic cell is active or depolarized.

If the classic form of LTP is a mediator of fear conditioning, then blockade of NMDA receptors in the amygdala should have two consequences: 1. The establishment but not the expression of LTP in the amygdala should be disrupted, and 2. the acquisition but not the expression of fear conditioning should be disrupted. Existing data are, for the most part, consistent with this line of reasoning. Recent studies have shown that LTP induced in the amygdala by stimulation of the endopyriform nucleus is dependent on NMDA receptors (Gean et al 1993). However, induction of LTP in the same regions by stimulation of the external capsule does not exhibit the same dependence (Chapman & Bellavance 1992). Regardless, these studies have focused on the basal nucleus, which is not necessarily the only or even the main site of plasticity in fear conditioning (recall that the cells receiving CS-US convergent inputs are in the lateral nucleus). Further, these studies have not stimulated known CS or US pathways in their LTP paradigms. Although LTP has been demonstrated in a CS pathway to the lateral amygdala, the thalamo-amygdala auditory pathway (Clugnet & LeDoux 1990), the pharmacology of LTP in this pathway has yet to be determined. Blockade of NMDA receptors in the lateral/basal amygdala interferes with the acquisition but not the expression of Pavlovian fear conditioning to a CS (e.g. Miserendino et al 1990) or to contextual stimuli (Fanselow & Kim 1994). Because of the small size of these brain areas it is not possible to conclude whether the site of action is in the lateral or basal nucleus. Nevertheless, NMDA receptors in this region seem to be involved.

SUMMARY   Important steps have been taken toward understanding the cellular basis of fear conditioning. While much work remains, this is a young research area and it holds great promise for elucidating mechanisms through which an important aspect of emotional learning occurs. Findings to date are consistent with the view that an NMDA-dependent, LTP-like phenomenon in the amygdala might mediate fear conditioning, but this remains unproved.

Extinction of Conditioned Fear

Extinction is the process through which the strength of a conditioned response is weakened by repeated exposure to the CS in the absence of the US. Considerable evidence suggests that extinction of conditioned fear does not occur passively (i.e. the memory persists in the absence of explicit extinction training), and when extinction occurs it is not passive forgetting but instead is an active process, quite possibly involving new learning (Bouton & Swartzentruber 1991). Further, conditioned fear reactions are notoriously difficult to extinguish and once extinguished they can recur spontaneously or can be reinstated by stressful experiences (e.g. Rescorla & Heth 1975, Jacobs & Nadel 1985, Campbell & Jaynes 1966). Because fear conditioning processes may contribute to such disorders as phobia, excessive fear, anxiety, posttraumatic stress, and panic, understanding how the effects of fear conditioning are modulated by extinction is of great clinical interest.

The neural basis of extinction has been studied much less extensively than has the neural basis of acquisition, but some key discoveries have been made. Although cortical areas are not required for the acquisition of conditioned defense (see above), cortical lesions can interfere with extinction. For example, lesions of auditory (Teich et al 1989) or visual (LeDoux et al 1989) cortex have no effect on simple conditioning involving an auditory or visual CS. However, with such lesions extinction is greatly prolonged if not prevented. This suggests that the subcortical sensory projections to the amygdala mediate learning in this situation (since the relevant cortical areas have been removed) and that subcortical learning of this type is relatively indelible (LeDoux et al 1989). The cortical lesions, in other words, may have unmasked the existence of relatively permanent memories. Extinction, by this account, might be a process by which the cortex regulates the expression of these indelible memories. A recent study failed to replicate these effects (Falls et al 1992), but a number of procedural differences between the studies might be responsible for the failure to replicate.

Additional studies have shown that extinction is prolonged by damage to the medial prefrontal cortex (Morgan et al 1993), which may be the link between sensory cortex and the amygdala in behavioral extinction. That is, the medial prefrontal cortex may modulate the expression of defense responses at the level of the amygdala. A related conclusion was reached on the basis of

studies recording unit activity in the prefrontal cortex and the amygdala during appetitive conditioning (e.g. Thorpe et al 1983, Rolls 1992).

Blockade of NMDA receptors in the amygdala interferes with the extinction of conditioned fear (Falls et al 1992). This reinforces the view that extinction is not passive forgetting but an active form of learning and suggests that NMDA-dependent synaptic plasticity may be involved. The synapses between the frontal cortex and the amygdala might be the plastic synapses in this case. Although extinction plasticity may involve modifications in the strength of the existing associations, extinction plasticity may also involve changes in the propensity with which existing memories are expressed.

Conditioned Fear and Instrumental Action (Coping)

A stimulus that warns of impending danger elicits defense responses, such as those discussed above, but it also has other consequences. Once the organism is acted on by the CS, it then prepares to act back on the environment, figuring out how to escape and/or avoid danger and the stimuli that are associated with danger. These instrumental emotional responses, which might be thought of as coping responses (Lazarus 1966, 1991), have been studied experimentally using avoidance conditioning procedures. Fear conditioning is generally assumed to be the first step in the learning of avoidance (e.g. Mowrer 1960, Mackintosh 1983). That is, the state of conditioned fear is assumed to be unpleasant or undesirable, and in the effort to reduce fear, the organism learns to escape from and ultimately avoid situations or stimuli that lead to the arousal of fear. It might therefore be expected that damage to the amygdala, which will prevent fear conditioning, would interfere with avoidance conditioning.

The literature on the effects of brain lesions on avoidance conditioning is large and fairly confusing, and is not reviewed in detail here. Several features of this literature are highlighted below.

First, many studies of active and passive avoidance demonstrate that lesions of the amygdala interfere with the acquisition of avoidance responses (Panksepp et al 1991, Sarter & Markowitsch 1985). It is not clear why some studies fail to find this effect, but an analysis of the underlying task demands might be revealing. Even for those tasks in which the amygdala is involved, the input and output connections and intra-amygdala circuitry are not very well understood, possibly because of the variability in the eliciting stimulus conditions and in the emitted instrumental responses. At the same time, the simplicity of the eliciting stimuli and elicited responses in fear conditioning probably contribute to the greater success achieved in uncovering brain mechanisms with this procedure.

Second, most studies of passive avoidance find that the septo-hippocampal system is important. This observation provides part of the conceptual foundation for Gray's septo-hippocampal theory of fear and anxiety (Gray 1982, 1987). Although the theory is based on an impressive survey of the literature, it is unclear to what extent the septo-hippocampal system is involved in the fear part or in the stimulus processing (e.g. contextual processing) aspect of many passive avoidance tasks. As noted above, the hippocampus is involved in fear conditioning if the CS is the context in which the US occurs rather than a discrete signal. The same may be true of passive avoidance, in which diffuse contextual cues usually serve as the Pavlovian CS. Other aspects of the septo-hippocampal model of anxiety have been discussed elsewhere (see commentaries in Gray 1982, LeDoux 1992, Panksepp 1990).

Third, although the amygdala is often required for the acquisition of avoidance, it is less important and probably unnecessary for the long-term maintenance of well-trained avoidance responses. Thus, after learning is established, the defense system involving the amygdala is no longer a necessary part of the avoidance circuitry. It is thus important to keep the phase of training in mind when asking questions about brain involvement in avoidance.

Fourth, the instrumental aspects of avoidance, unlike the Pavlovian elicited responses, may require connections between the amygdala and the ventral striatum for their acquisition and/or expression (Everitt & Robbins 1992). In particular, the nucleus accumbens of the ventral striatum may be a crucial area for the initiation and control of instrumental responses motivated by either appetitive or aversive processes, possibly resulting from its innervation by dopaminergic pathways.

In summary, although the literature on avoidance is somewhat confusing, studies of avoidance conditioning, like studies of fear conditioning, point to the amygdala as probably playing some role. This should not be surprising since avoidance conditioning is believed to involve Pavlovian fear conditioning (which requires the amygdala) followed by the learning of the instrumental avoidance response. The amygdala almost certainly contributes to the Pavlovian part of avoidance learning but its role in the instrumental part is less clear.

Fear Conditioning: Conclusions

Studies of fear conditioning have successfully identified the neural system that underlies this important form of learning and memory process. Part of the reason that researchers have been so successful is that in fear conditioning, simple, well-defined stimuli can be used to elicit stereotyped or at least repeatable responses that require little training. It is always much easier to trace neural pathways when the stimulus and the response can both be precisely

identified and quantified. This probably accounts for the greater success of studies of fear conditioning than of studies of avoidance conditioning in mapping the pathways of fear. At the same time, we have to be aware that the brain mechanisms of fear conditioning may not generalize to all aspects of fear. Whether fear of failure or fear of authority or fear of being afraid are mediated by the same basic system, with some cognitive baggage added on, remains to be determined.

Relation of the Neural Basis of Fear to Other Emotions

As noted above, the neural basis of fear conditioning has been studied so extensively and successfully because there are good techniques available for eliciting and quantifying conditioned fear responses. For the same reason, there has been a relative paucity of research on the neural basis of most other emotions, especially positive emotions.

Some studies have examined the neural basis of positive affective reactions and approach behavior. Unlike studies of defensive behavior, which are relevant to the emotion of fear, these studies are less specifically related to a well-defined emotion, except possibly pleasure. Most of this work has involved three paradigms: brain stimulation reward (Rolls 1975, Olds 1977, Gallistel et al 1981), stimulus-reward association learning procedures (see Aggleton & Mishkin 1986, Gaffan 1992, Everitt & Robbins 1992, Rolls 1992, Ono & Nishijo 1992), and appetitive classical conditioning (Gallagher & Holland 1992). The neural network underlying these tasks overlaps somewhat with the fear system in that the amygdala is involved to some extent in each of these tasks [but see Cahill & McGaugh (1990) for a comparison of the relative contribution of the amygdala to appetitive and aversive learning]. Unfortunately, the neural system is poorly understood for these positive emotional phenomena and much more work is needed. The creation of new models of positive affect is also important.

Given that the amygdala is involved to some extent in both positive and negative emotional reactions, one might be tempted to conclude that the amygdala is the centerpiece of an emotional system of the brain. However, this would be a mistake. We know far too little about the neural system–mediating emotions other than fear and far too little about variants of fear other than simple forms of conditioned fear. The amygdala is a sufficiently complex brain region that it could be involved in fear and reward processes in completely different ways and for different reasons. Other attempts at identifying emotion with a single system of the brain (e.g. the limbic system) have fared poorly (see LeDoux 1991), and we should be cautious not to overinterpret the role of the amygdala.

IMPLICATIONS OF THE NEURAL BASIS OF FEAR FOR UNDERSTANDING EMOTION

Examining emotion from the point of view of the nervous system allows us to see questions about this complex process from a unique angle. Several issues have been raised about the nature of emotion in light of the neural systems analysis of emotion just presented.

Cognitive-Emotional Interactions

The nature of cognitive-emotional interactions is one of the most debated topics in the psychology of emotion (e.g. Zajonc 1980, 1984; Lazarus 1982, 1984, 1991; Mandler 1984; Leventhal & Scherer 1987; Frijda 1986; LeDoux 1987, 1993b; Parrott & Schulkin 1993a,b; Izard 1992; Oatley & Johnson-Laird 1987; Ortony et al 1988; Ekman 1992). Knowledge of the neural system underlying emotion can help constrain our thinking on this topic. As we have seen, the system that mediates the emotion fear is well characterized. We can thus examine how cognitive processes participate in and interact with the neural system of fear.

DEPENDENCE OF EMOTIONAL PROCESSING (APPRAISAL) ON COGNITION   By most accounts, the amygdala plays a crucial role in deciding whether a stimulus is dangerous or not. Functions mediated by the amygdala are likely to be the neural instantiation of the emotional process know as appraisal (Arnold 1960, Lazarus 1966, 1991; Ekman 1977, 1992; Leventhal & Scherer 1987, Ellsworth 1991, Scherer 1991), at least for the appraisal of danger. The anatomical inputs to the amygdala from systems involved in stimulus processing define the kinds of events that can be appraised by the amygdala and the kinds of cognitive factors that might be important in this evaluation.

For example, the amygdala receives inputs from sensory processing areas in the thalamus and cortex (summarized in Figure 1; see LeDoux 1992 for review). The former provide course representations, but reach the amygdala quickly, while the latter provide detailed stimulus information, but reach the amygdala more slowly because of the additional processing stations involved at the cortical level. The thalamic inputs thus may be useful for producing rapid responses on the basis of limited stimulus information, whereas cortical inputs are required to distinguish between stimuli. Rapid response to danger has obvious survival value (Ohman 1986, 1992; Ekman 1992; LeDoux 1986, 1990), suggesting the possible significance of a quick-and-dirty subcortical pathway. The amygdala also receives inputs from the hippocampal formation (Ottersen 1982, Amaral et al 1992). These set the context in which an emotional stimulus is to be evaluated (Phillips & LeDoux 1992b, Kim & Fanselow 1992, Selden et al 1991, Penick & Solomon 1991, Good & Honey 1991),

possibly allowing the amygdala to respond to a stimulus as threatening in one situation and not in another. In addition, given the role of the hippocampus in declarative or explicit memory (Squire 1992, Eichenbaum 1992), the hippocampal inputs may also allow fear responses to be activated by explicit or conscious memories of past experiences. When the functions of the other cortical areas that project to the amygdala have been elucidated we will be able to make additional predictions about the kinds of inputs that the amygdala appraises.

The anatomical organization of the fear system thus tells us that emotional responses can be elicited by processing in a wide range of systems. The issue of whether emotional processing is dependent on prior cognitive processing is reduced to a question of how we define cognition. If cognition is defined broadly to include sensory information processing, such as that occurring in the sensory thalamus and/or sensory cortex, as well as the processing that occurs in complex association areas of cortex in the frontal lobes or hippocampus, then emotional processing by the amygdala is highly dependent on cognitive processing. If cognitive processing is defined narrowly to include only the higher mental functions most likely mediated by complex association cortex, then emotion is not necessarily dependent on prior cognitive processing.

Emotional responses also might occur in the absence of inputs from cognitive systems. On the one hand, the amygdala receives inputs about the state of various internal organs of the body (e.g. Cechetto & Calaresu 1984) and these subcortical sensory inputs, like other exteroceptive sensory inputs, might be capable of triggering emotional responses. It is known that internal signals can precipitate emotional reactions, as in panic attacks (Klein 1993), but it is not known whether the coding of the signal by the amygdala is involved. On the other hand, in some situations spontaneous discharges of the amygdala might generate emotional responses, but little evidence supports this possibility.

In the past, cognitive-emotional interactions have often been discussed without much consideration of what the terms cognition and emotion mean. I have limited this discussion to the emotion of fear and have examined how specific cognitive processes (such as sensory processing in the thalamus, perceptual processing in the neocortex, spatial and contextual processing in the hippocampus, or mnemonic processing in the hippocampus) can influence the amygdala and thereby elicit fear responses. This perspective forces us to abandon discussions of cognitive-emotional interactions in terms of vague monolithic cognitive processes and instead consider exactly which cognitive processes are involved in fear reactions. This is a more practical and tractable problem than the problem of how cognition and emotion, in the broader sense of the terms, interact. All we have to do is to determine how a particular cognitive process is organized in the brain and then determine how that brain

region interacts with the amygdala. We can then hypothesize the nature of that particular cognitive-emotional interaction, at least within the fear domain.

EMOTIONAL INFLUENCES ON COGNITION   A similar situation holds for the other side of the cognitive-emotional dyad. That is, we can examine projections from the amygdala to areas involved in cognitive processing and make predictions about how the appraisal of danger by the amygdala might affect these processes (see Figure 3). The role of these projections in information processing has not been studied empirically, but the anatomical observations are suggestive of the functions served. For example, the amygdala projects back to the cortical sensory processing systems that send projections to the amygdala (Price et al 1987, Amaral et al 1992). Although the amygdala receives inputs from only the later stages of sensory processing, its back projections innervate the earlier stages as well. These projections from the amygdala to sensory processing areas may allow the amygdala's appraisals of danger to influence ongoing perceptions of the environment (Rolls 1992, LeDoux 1992). The amygdala does not project back to the thalamus, but the cortical areas that receive amygdala inputs do,
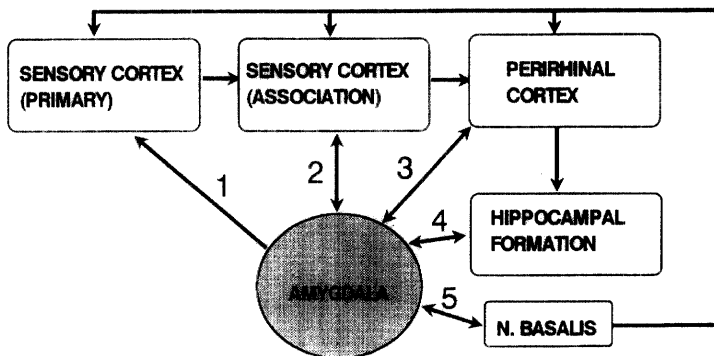

Figure 3 Amygdala influences on cortical cognitive processing. Once an emotional stimulus activates the amygdala, the amygdala can in turn impact cognitive processes organized in the neocortex. The amygdala receives inputs from sensory association areas but not primary sensory cortex (see Figure 2). However, it appears to project back to primary sensory cortex (1) and to association areas (2). These projections allow the amygdala and its coding of emotional significance to control the ongoing flow of sensory information and may represent channels by which emotional processing can influence perception. The amygdala receives inputs from and projects to the perirhinal cortex and hippocampal formation (3, 4). These structures have been implicated in explicit or declarative memory processing and the interconnections may account for emotional influences on memory processing. The hippocampus is also important in adding context to emotional situations, and the interconnections between the amygdala and the hippocampus may play a role in making context an emotional stimulus. The nucleus basalis (N. Basalis) is the source of cholinergic inputs to widespread areas of the cortex (5) and plays an important role in cortical arousal and attention. Projections from the amygdala to this region may be important in attention and arousal processes.

allowing for an indirect modulation of thalamic processing. Additionally, the amygdala projects to the nucleus basalis (Price et al 1987, deOlmos et al 1985), which provides widespread cholinergic modulation of cortical arousal. These projections may allow the amygdala to participate in selective attention (Weinberger 1993, Kapp et al 1992, Gallagher & Holland 1992). The amygdala also projects to the hippocampus (Amaral et al 1992, Price et al 1987), allowing the appraisal of danger to modulate hippocampal functions, including spatial behavior (O'Keefe & Nadel 1978, O'Keefe 1993, McNaughton & Barnes 1990, Muller et al 1991), contextual processing (Phillips & LeDoux 1992b, Kim & Fanselow 1992, Selden et al 1991, Nadel & Willner 1980, Good & Honey 1991, Penick & Solomon 1991), and explicit or declarative memory storage or retrieval (Squire 1992, Eichenbaum 1992). Many other examples could be given, but these illustrate the usefulness of a neuroanatomical perspective in suggesting predictions about the nature of cognitive-emotional interactions.

IS EMOTIONAL PROCESSING COGNITIVE PROCESSING?   It has been argued that appraisal involves information processing; therefore, emotion is cognition (Lazarus 1982, 1984). However, as Zajonc (1984) and Izard (1992) have noted, cognitive processing is but one example of information processing. Noncognitive biological information processing systems include the immune system and the genome. Just because emotion involves information processing does not mean that emotion is cognition.

The issue, again, depends on how cognition is defined. It can be defined to include emotion, motivation, and similar processes, but this would seem to defeat the purpose of having a designation of cognition as opposed to the more general term mind. Hilgard (1980) has reminded psychology that cognition historically has been thought of as part of a trilogy of mind that also includes emotion and will (motivation) rather than as an all-encompassing description of mind. Certainly, early pioneers of cognitive science did not view emotion as a cognitive process. According to Neisser (1967), emotion was one of the many aspects of psychology not included in the cognitive approach.

Studies of the processing rules and transformations in areas of the brain that are involved in cognition and areas involved in emotion might be able to address the question of whether emotional and cognitive processing are fundamentally different. Studies of the brain mechanisms of emotion have pointed to the amygdala as an important part of an aversive emotional memory system, and to the hippocampus as part of the system involved in cognitive or declarative form of memory (for a discussion of emotional and cognitive memory systems, see LeDoux 1993a). This does not prove that the systems operate by different information processing rules, but it certainly leaves open the possibility. For example, given that cells in the amygdala and hippocampus both "learn" during conditioning, one might ask whether comparable repre-

sentations are encoded. Although a lot has been learned about the nature of hippocampal information processing from studies of the physiology of hippo-campal neurons (for review, see O'Keefe 1993), we know very little about how amygdala neurons process information. If and when physiological studies of the amygdala catch up with studies of the hippocampus, it may be possible to determine whether these systems use different processing rules or whether they simply do different things on the basis of similar processing functions.

Conscious versus Unconscious Processes in Emotion

The issue of what is conscious or unconscious in emotion was around even before James (1884) popularized it with his famous question about whether we run from a bear out of fear (conscious or subjective emotion) or whether fear comes from running away. However, all animals, invertebrates as well as vertebrates, must have a way of defending themselves from danger. When a fruitfly is conditioned to avoid shock by flying out of the chamber where the shock occurred (Tully 1991), it is unlikely that a conscious state of fear intervenes between the reception of the stimulus and the production of the response. Comparative psychologists long ago learned the importance of parsi-mony in explaining findings across species. If we do not need subjective fear to explain defensive responses in lower species, then we should not explain defensive responses in higher species in this way either. At least amongst vertebrates, the neural system involved in detecting danger and producing defense responses is similarly organized in all species studied. This suggests that evolution long ago figured out how to organize the defense system and has continued to use this organizational blueprint. Subjective fear, in this view, is what occurs when the evolutionary old defense system is activated, but only in a species that also has the capacity for subjective conscious states.

   This view highlights the value of studies of experimental animals in under-standing emotional systems. Because the system that generates emotional responses is strongly conserved in evolution (the amygdala and its connections are involved in all vertebrates studied), we can learn about human defense or fear reactions by studying other creatures. And if fear responses and conscious emotional states of fear are the result of activation of an evolutionarily con-served system that detects danger, then studying how the neural system pro-duces fear responses in animals will also shed light on mechanisms that contribute to conscious states of fear in humans.

Volitional Control of Emotion

Whether emotional responses are under voluntary control is an important issue with a great deal of practical application to legal issues. What seems clear from the neural systems perspective is that there are both involuntary and voluntary

responses, each mediated by different neural networks emanating out of the amygdala.

Many defense responses are respondents rather than operants. That is, the responses are controlled by their antecedents rather than by their consequences (Bouton & Bolles 1980). Borrowing a term from ethology, these responses are released by the presence of stimuli that have their releasing capacity either as a result of genetic programming or associative learning processes. These responses are, in the language of cognitive psychology, effortless and automatic, and probably are controlled by unconscious appraisal processes. These involuntary emotional responses include behavioral (e.g. freezing and flight reactions, facial expressions) as well as visceral (e.g. autonomic and endocrine) responses.

Emotional respondents are only part of the story of emotional responsivity. Once emotional respondents are expressed, emotional operants begin to occur. These are instrumental responses. A rat exposed to a cat will automatically freeze in order to minimize the possibility of an attack. During the freezing episode, the rat begins planning strategies that might lead to successful escape, using information stored from past experience and expectations about possible outcomes. These kinds of processes are related to what has been called risk-assessment behavior (Blanchard et al 1993). This may be the point at which Gray's (1982, 1987) septo-hippocampal system (which may be involved in the instrumental and cognitive phase of fear and anxiety) meets the amygdala-based system (which is probably more involved in the automatic, elicited aspects of fear and anxiety).

Respondents are not learned. They are hard-wired into the nervous system, and are subject to Pavlovian conditioning. But conditioning does not modify the responses; it allows new stimuli to activate the responses. In contrast, emotional operants are learned through instrumental (operant) conditioning procedures. Although the respondents are controlled by outputs of the amygdala to brainstem motor systems, the instrumental actions (such as escape and avoidance) appear to be mediated by projections from the amygdala to a forebrain region know as the ventral striatum (Everitt & Robbins 1992), an important link to the extrapyramidal motor system. The emotional respondent system has been examined in detail, but less is known about emotional operants, which are much more difficult to study because they are considerably more complex. However, this is an important area for future research because it may help shed light on emotional coping responses (Lazarus 1991).

Psychopathological Issues

Disorders of fear regulation make up an important set of psychopathologic conditions. To the extent that we understand the anatomy of these systems, we will be in a better position to develop more selective drug therapies that are

targeted for the specific brain networks involved in fear regulation. In addition, knowledge of the anatomy of fear may help us understand some other aspects of pathological fear, and perhaps other emotions, as well.

The anatomy of the fear processing system tells us that fear can be triggered by many different kinds of information processing functions that lead to the amygdala. If, for genetic or experiential reasons, the lower-order pathways are more efficient at triggering the amygdala than are the higher-order pathways in some individuals, we would expect those individuals to have rather limited insight into the nature of their emotional reactions. People have different degrees of insight into their emotions and the anatomical findings suggest a possible explanation.

Another point to consider is that emotional memories mediated by the amygdala system are indelible. That is, the memories persist even after emotional behavior is extinguished. This has been demonstrated in behavioral studies (e.g. Bouton & Swartzentruber 1991), but is also illustrated dramatically by studies showing that with cortical lesions, extinction can be prolonged or eliminated (Teich et al 1989, LeDoux et al 1989, Morgan et al 1993). Extinction thus appears to involve cortical inhibition of indelible, amygdala-mediated memories. It is not a process of emotional memory erasure. The role of therapy may be to allow the cortex to establish more effective and efficient synaptic links with the amygdala.

Finally, consider the issues of infantile amnesia and the inaccessibility of memory for early trauma. Jacobs & Nadel (1985) made the intriguing suggestion that our inability to remember early experiences may be because the hippocampus is not sufficiently mature to allow us to form declarative or conscious memories until around the second or third year of life. They suggest that early trauma might not be accessible consciously because the system that encodes conscious memories is not fully functional. At the same time, we know that early trauma can have long lasting influences on behavioral and mental states, which suggests that the system that encodes these unconscious traumatic memories is present and functional. We know that the amygdala is crucial for at least some forms of aversive or traumatic learning and memory, but little definitive work has been done on the maturational time course of the amygdala that would allow us to clearly state whether it develops before the hippocampus. However, a recent study showed that rats can be conditioned to an auditory CS at an earlier age than they can to contextual stimuli (Rudy 1993). This finding implies strongly that the amygdala matures earlier than does the hippocampus.

There are several implications of these observations. First, early memories may be emotional memories (and not explicit, declarative conscious memories) because the emotional memory system (and not the declarative system) is functional at the time. Second, early emotional memories, including traumatic

as well as nontraumatic memories, may be inaccessible to consciousness not because of active repression but because of the time course of brain maturation. Third, the extent to which one can gain conscious access to these early memories, which were encoded in the absence of the conscious or declarative memory system, may be limited.

CONCLUSIONS

Progress in understanding the neural basis of fear has been rapid in the last decade. We now understand the anatomy of this system in great detail. This information can help us see emotions in a different light and suggests some insights and constraints concerning important issues about the nature of emotion. Although much remains to be done, especially in terms of determining the generality of the findings, we are well on the way to understanding how one important aspect of emotional life is represented in the brain.

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