Fear and the Brain: Where Have We Been, and Where Are We Going?

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In recent years, there has been an explosion of interest in the neural basis of emotion. Much of this enthusiasm has been triggered by studies of the amygdala and its contribution to fear. This work has shown that the amygdala detects and organizes responses to natural dangers (like predators) and learns about novel threats and the stimuli that predict their occurrence. The latter process has been studied extensively using a procedure called classical fear conditioning. This article surveys the progress that has been made in understanding the neural basis of fear and its implications for anxiety disorders, as well as the gaps in our knowledge. Biol Psychiatry 1998;44:1229–1238

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Introduction

Twenty years ago, emotion was hardly talked about in neuroscience circles. Today, it is one of the hot topics in the field. The transformation has come because research on one emotion, "fear," has been enormously successful in mapping the pathways and even in explaining some of the cellular mechanisms involved.

The key to the fear pathways in the brain is a small region called the amygdala. Damage to this area greatly changes the way animals, including people, act in the face of danger. Monkeys, for example, lose their fear of snakes, and rats their fear of cats, as a result of amygdala damage. Damage to the amygdala prevents rats and people from learning about stimuli that warn of danger.

The amygdala has in fact become quite popular as a research topic. A quick scan through various journals in the field reveals more and more papers on the structure and function of the amygdala each year. It is perhaps a sign of the times that the amygdala and its contribution to emotional behavior have even penetrated deep into popular culture. My two sons were watching Batman on The Cartoon Network the other day when I fell victim to the "cocktail party phenomenon," where your attention is grabbed by something significant that you were not paying attention to. All of a sudden, I heard the words, "the amygdala," which was described as "an almond-shaped mass of nerves in the brain that controls feelings of rage." I turned to the screen. In the story, the amygdala of Aaron Helzinger had been removed in an attempt to calm him, but instead he was transformed into a creature of perennial rage called "Amygdala." Actually, I did not remember all these details, but a quick trip to the Worldwide Web led to a site that had all the facts, and even guided me to the issue of the printed version of Batman that the show was based on. The search also revealed a site that promised to show you how to "click your amygdala" by exposing yourself to certain kinds of stimuli.

Given all this interest in the amygdala, it seems like a good time to take stock of where we are in this field. Below, I will review the basic facts, consider some controversies, and preview some new directions.

Fear, Anxiety, and Fear Conditioning

Fear is a normal reaction to threatening situations and is a common occurrence in daily life. When fear becomes greater than that warranted by the situation, or begins to occur in inappropriate situations, a fear or anxiety disorder exists (e.g., Marks 1987; Öhman, 1992). Excluding substance abuse problems, anxiety disorders account for about half of all the conditions that people see psychiatrists for each year (Manderscheid and Sonnenschein 1994). It seems likely that the fear system of the brain is involved in at least some anxiety disorders (LeDoux 1996; Öhman 1992), and it is thus important that we understand in as much detail as possible how the fear system works. This information may lead to a better understanding of how anxiety disorders arise and how they might be prevented or controlled. If studies of the fear system shed light only on fear and no other emotion, that alone would be an important achievement.

There are a number of experimental tools for studying fear and anxiety; however, one of the simplest and most straightforward is classical fear conditioning. In fear conditioning, a relatively neutral stimulus (the conditioned stimulus, CS) is paired with an aversive event. In a typical study, a innocuous tone is paired with a mild foot shock. After very few pairings (as few as one under certain

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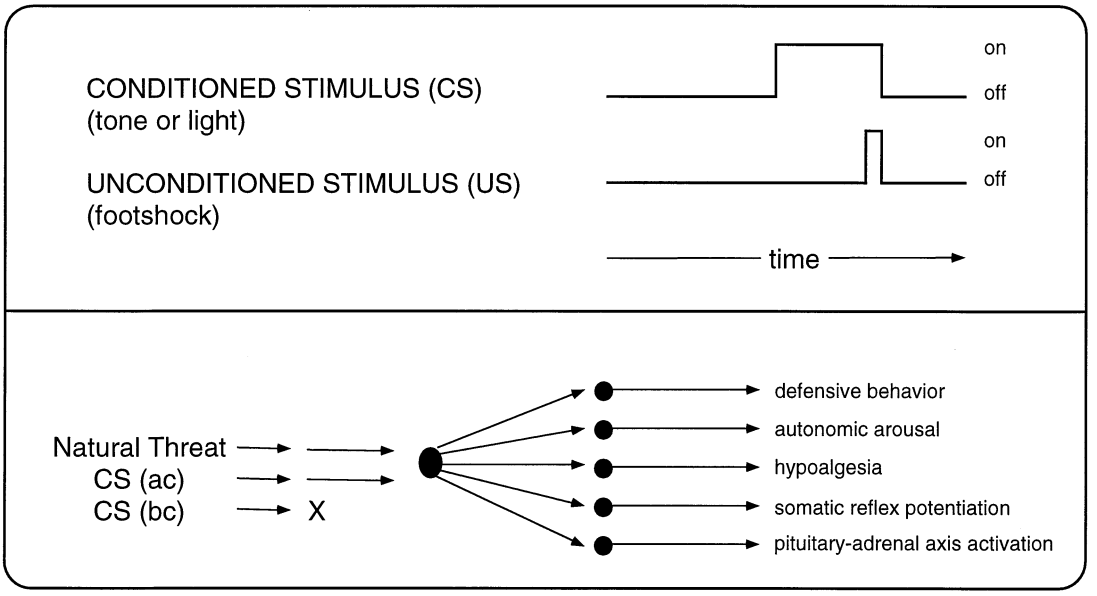

Figure 1. Fear conditioning involves the temporal pairing of an innocuous conditioned stimulus (CS), such as a light or tone, with a noxious unconditioned stimulus, typically foot shock (above). After conditioning (ac), but not before (bc), the CS enters fear networks and activates defense systems typically activated by a natural threat, such as a predator (below).

conditions) long-lasting changes are established in the brain, such that the CS comes to elicit behavioral, autonomic, and endocrine responses that are characteristically expressed in the presence of danger (Figure 1). The responses tend to be hard-wired, species-typical expressions of fear, and are not learned or conditioned. Fear conditioning, in other words, does not involve response learning, but instead involves the coupling of new stimuli to preexisting responses. Fear conditioning occurs throughout the phyla, and within the vertebrates, it appears that very similar neural mechanisms are involved across species. Much of the relevant background information about fear conditioning is summarized in LeDoux (1996).

Fear conditioning may not tell us all we need to know about all aspects of fear, or all aspects of fear or anxiety disorders, but it is an excellent starting point. Furthermore, many of the other fear assessment procedures, such as the various forms of avoidance conditioning, crucially involve an initial phase of fear conditioning that then provides motivational impetus for the later stages of instrumental avoidance learning (e.g., Mowrer 1939; Dollard and Miller 1950). Other fear assessment procedures do not require learning (e.g., the open field, the elevated maze, or light avoidance), but these are somewhat less amenable to a neural systems analysis than fear conditioning, due mainly to the fact that the fear-eliciting stimulus is often poorly defined in these procedures. Also, since many of the things that people fear are learned about through experience, an understanding of how fear learning occurs is an important part of an understanding of the fear system.

What Are the Brain Pathways Involved in Fear Conditioning?

Simply stated, the pathways underlying fear conditioning involve the transmission of CS information to the amygdala, and transmission from the amygdala to various conditioned response (CR) control networks in the brain stem. Several different CS modalities have been used (e.g., auditory, visual, olfactory), but I concentrate below on studies using the auditory modality, since the pathways to the amygdala are best understood for these (Figure 2).

An acoustic CS is transmitted through the auditory system to the level of the auditory thalamus, the medial geniculate body (MGB), and is then transmitted to two disparate targets. One is the amygdala and the other is the auditory cortex. Auditory cortical areas in turn project to the amygdala (Price et al 1987; Amaral et al 1992; LeDoux et al 1990a, 1990b; Turner and Herkenham 1991; Romanski and LeDoux 1993a, 1993b; Mascagni et al 1993). The auditory thalamus is believed to provide rapid but imprecise information, whereas the auditory cortex provides a somewhat delayed (relative to the thalamus) but more detailed representation to the amygdala (e.g., LeDoux 1986, 1996). Although damage to the auditory cortex before conditioning does not prevent conditioning to a single tone (e.g., Romanski and LeDoux 1992a, 1992b; Campeau and Davis 1995b), the auditory cortex appears to be required for some aspects of conditioned responding to more complex stimulus situations (e.g., Jarrell et al 1987), though the exact conditions requiring

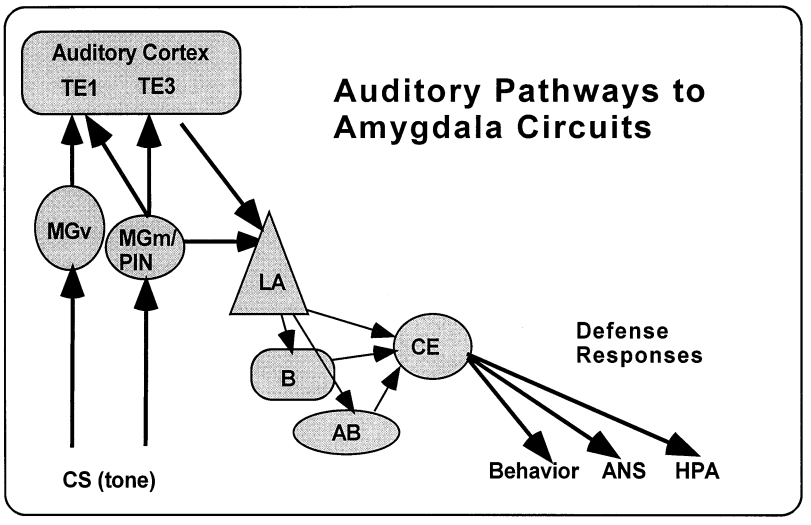

Figure 2. The basic neural pathways underlying fear conditioning involve transmission of sensory stimuli about a conditioned stimulus (CS) to the amygdala from the thalamus and cortex and the control of emotional responses by outputs of the amygdala. The illustration shows auditory signals from the thalamic nuclei (MGm/PIN) and auditory cortex (TE3) reaching the lateral nucleus of the amygdala (LA). LA then projects to the central nucleus (CE) directly and by way of intra-amygdala pathways involving the basal (B) and accessory basal (AB) nuclei. CE, in turn, controls the expression of defense responses, including behavioral, autonomic nervous system (ANS), and hormonal (HPA, hypothalamic–pituitary–adrenal axis) responses.

the auditory cortex are poorly understood (see Armony et al 1997).

Anatomical and physiological studies suggest that the lateral nucleus of the amygdala (LA) is a major site of termination of both thalamic and cortical auditory inputs (LeDoux et al 1990a, 1991; Clugnet et al 1990; Turner and Herkenham 1991; Bordi and LeDoux 1992; Romanski et al 1993; Romanski and LeDoux 1993a; Mascagni et al 1993; Amaral et al 1992; Price et al 1987). In fact, single cells in LA receive convergent inputs from the auditory thalamus and cortex (Li et al 1996). The central nucleus (CE), on the other hand, appears to be the interface with motor systems involved in controlling conditioned responses (LeDoux 1992; Kapp et al 1992; Davis 1994). Thus, whereas lesions of CE interfere with the expression of fear responses of all types, lesions of areas to which CE projects interfere with select responses. For example, lesions of the lateral hypothalamus interfere with sympathetic nervous system mediated responses (like changes in blood pressure), whereas lesions of the central gray interfere with behavioral conditioned responses (like freezing).

Information flows from LA to CE over well-defined intra-amygdala circuits (e.g., Price et al 1987; Amaral et al 1992; de Olmos et al 1985; Pitkänen et al 1997; Smith and Paré 1994). For example, inputs arriving in LA are distributed to the basal (B), accessory basal (AB), and CE nuclei, and to a lesser extent to several other areas (Pitkänen et al 1995). The B and AB nuclei also project to CE (Savander et al 1995, 1996a; Paré et al 1995). Figure 2 illustrates some of the key pathways. Damage to LA and CE (but not other amygdala nuclei) disrupts fear conditioning to a tone CS (LeDoux et al 1990b; Majidishad et al 1996), suggesting that the direct projection from LA to CE is sufficient to mediate conditioning.

The identification of the amygdala as a key site of fear processing and fear learning has obvious implications for understanding anxiety disorders. It is conceivable that alterations in the way the amygdala processes information underlie at least some of these conditions. In addition, some cortical regions that project to the amygdala have been implicated in aspects of fear conditioning, and these finding also have implications for understanding anxiety disorders. Two of these areas include the hippocampus and its role in contexual conditioning and the medial prefrontal cortex and its role in extinction. When rats are conditioned to a tone paired with a shock, they also develop fear responses to the chamber in which the tone–shock pairings occur. The chamber cues are part of what is referred to as the conditioning context. Damage to the hippocampus interferes with conditioning to the chamber or contextual cues (Phillips and LeDoux 1992; Kim and Fanselow 1992; Selden et al 1991; Blanchard et al 1970). It is possible that the generalization of fear that occurs in some anxiety disorders is due to weakening of contextual constraints on fear. The fact that stress, a concomitant of anxiety disorders, impairs the anatomy, physiology, and behavioral functions of the hippocampus (Sapolsky 1996; McEwen and Sapolsky 1995) is consistent with this. Extinction refers to loss of the ability of the conditioned stimulus to

elicit fear responses after repeated presentations in the absence of the shock. Damage to the medial prefrontal cortex results in a prolongation of extinction (Morgan et al 1993; Morgan and LeDoux 1995). This is important, since it seems to produce something akin to clinical fears—that is, fears that, once established, are difficult to get rid of. Stress also affects functions of the prefrontal cortex (Diorio et al 1993), suggesting that the alterations in this area may contribute to the irrational fears of patients with some anxiety disorders.

Some Controversies about the Circuitry

In spite of the general agreement about the neural circuitry of fear and fear learning (see LeDoux 1996; Davis 1994; Maren and Fanselow 1996; Kapp et al 1992), several controversies have arisen. A brief discussion of these is in order.

Recent studies have questioned the importance of LA as the site of CS reception in the amygdala (Killcross et al 1997); however, these studies employed a complex behavioral paradigm requiring hundreds of training trails, and the results are not directly relevant to our studies involving rapid acquisition over a few (1–5) trials. These issues are discussed in more detail in Nader and LeDoux (1997) and Killcross et al (1997).

Another controversial point is the sufficiency of the thalamoamygdala pathway in mediating learning (see Campeau and Davis 1995b). Studies involving lesions made after training and before testing question whether the thalamic pathway alone can sustain conditioning; however, several lines of evidence support the importance of the thalamic pathway. First, unit recording studies show that physiological changes occur in LA prior to the auditory cortex both within and across trials (Quirk et al 1995, 1997). Thus, plasticity clearly exists in the amygdala that cannot be explained by cortical transmission. Further, several functional imaging studies in humans have shown evidence for subcortical processing of masked visual emotional stimuli by the amygdala, including conditioned emotional stimuli (Whalen et al 1998; Buchel et al 1998).

A third controversy involves the question of whether the amygdala is a site of plasticity and storage or just a modulator of plasticity elsewhere. McGaugh and colleagues have argued that the amygdala just modulates plasticity in other areas (e.g., McGaugh et al 1995). That the amygdala modulates storage in other brain systems seems clear from numerous studies (reviewed by McGaugh et al 1995; Packard et al 1995; Gold 1995); however, the stronger conclusion—that plasticity and storage do not occur in the amygdala during aversive learning—is more problematic. This conclusion is based, in part, on the finding that lesions of the amygdala made within a few days of conditioning interfere with the expression of inhibitory avoidance learning, but lesions made 10–14 days later do not (see McGaugh et al 1995 for a discussion of this and other lines of evidence); however, inhibitory avoidance and fear conditioning differ procedurally and could also have different neural bases (see LeDoux 1996). Also, several studies (see above) have shown that plasticity occurs in the amygdala during fear conditioning (Quirk et al 1995, 1997; Armony et al 1998). An obvious question is whether the effects of amygdala lesions on fear conditioning are time-dependent. It turns out that they are not (Maren 1998); however, this may not be very interesting. Given that conditioned fear responses require the amygdala for their expression (Davis 1994; LeDoux 1992; Kapp et al 1992), it is not possible to distinguish effects of lesions on learning/memory processes as opposed to response expression (McGaugh et al 1995). To resolve this issue we used reversible inactivation of the amygdala during acquisition (Muller et al 1997). Infusion of the gamma-aminobutyric acid agonist muscimol into the lateral/basal amygdala during learning prevented learning from taking place. This was true for both the tone CS and for contextual stimuli. Further, the same animals, when retrained after the first test, learned just fine, showing the reversibility of the effects. For other studies related to this point, see Helmstetter (1992), Helmstetter and Bellgowan (1994). Why then might inhibitory avoidance and fear conditioning differ with respect to the role of the amygdala? There is an old literature suggesting that once avoidance is learned, the situation losses its emotional impact and the amygdala, although needed for initial learning, is not required to maintain avoidance performance (see LeDoux 1996). This sounds very similar to what goes on in inhibitory avoidance (amygdala is needed initially but not later). Conclusions based on inhibitory avoidance should not be freely generalized to fear conditioning.

Fourth, the role of the hippocampus in contextual conditioning has been questioned on two grounds. Hippocampal damage does not always impair context conditioning (Gisquet-Verrier and Doyere 1997; Phillips and LeDoux 1995; Maren et al 1997); however, this most likely is due to the use of conditions that bias the animal toward being conditioned to specific cues in the environment rather than to the context per se, thus allowing conditioning to proceed in ways that are independent of the hippocampus (see Phillips and LeDoux 1995). If lesions are made before training, animals are more likely to become conditioned to elemental cues, since they are unable to become conditioned to the context itself (Frankland et al in press). The inconsistency resulting from pretraining lesions may be due to inconsistency in the degree to which individual

animals become conditioned to elemental cues in the context or background when the hippocampus is damaged before learning. The second point of contention comes from studies suggesting that hippocampal effects on context conditioning, as measured by freezing behavior, are secondary to changes in activity levels produced by the lesions—more activity competes with freezing and drives down the scores, leading to a false result with respect to context (Good and Honey 1997; McNish et al 1997); however, there are a number of problems with this interpretation (for a discussion, see Maren et al 1998; McNish et al 1998). One problem is that hippocampal lesions have no effect on freezing to a tone CS measured by freezing. McNish et al argued that tone conditioning is stronger, and therefore resistant to competition by activity; however, during the early phase of training, when tone conditioning is weak, hippocampal lesions are still ineffective. Another problem is that for individual animals, the amount of general activity in a novel environment does not correlate inversely with the amount of freezing. In other words, although hippocampal lesions can lead to an increase in activity, the degree of increased activity does not predict the amount of freezing and cannot be the explanation for the freezing deficit.

Fifth, the effects of medial prefrontal cortex lesions on extinction, though replicated several times in our lab (Morgan et al 1993; Morgan and LeDoux 1995), have not been found in another study (Gerwitz et al 1997). Although the procedures used differed in the studies from the two labs, one would hope that the findings are sufficiently general to extend beyond a limited paradigm. That the findings may be more general is suggested by unit recordings in primates, which have indicated that the medial prefrontal cortex is crucially involved in breaking associations during reversal learning, which is similar to the process involved in extinction (Thorpe et al 1983). More work is needed to fully understand the contribution of the prefrontal cortex to extinction, which is important given the implications of such studies for elucidating the nature of clinically debilitating fears that resist extinction.

Where Is Research on Fear and the Amygdala Going?

Best Level of Analysis of the Amygdala

Our recent studies of the connections of the amygdala suggest that the organization of this brain region is determined not at the level of nuclei but at the level of subnuclei. For example, anatomical and physiological studies suggest that auditory information is received mainly by the dorsal subnucleus of the lateral nucleus (LeDoux et al 1990a; Bordi and LeDoux 1992), and that the medial subnucleus, which receives information from the dorsal subnucleus, gives rise to most of the intra-amygdala connections of the lateral nucleus (Pitkänen et al 1997). A similar condition holds for the other nuclei as well. Thus if we want to understand how the amygdala processes information, we will need to work at the level of the subnuclei rather than nuclei. This means that the traditional methods of placing lesions or injections of drugs that influence one nucleus at best, but typically several nuclei, are going to be of limited value. Other techniques, though, such as unit recordings, have sufficient resolving power to be useful at this level of analysis.

Contribution of Unit Recordings

The validity of the subnuclear organization of the amygdala, revealed by anatomical tracing studies, is verified by unit recordings. Short-latency auditory responses are only found in the dorsal subregion of the lateral nucleus, and many of these cells are responsive to both auditory (CS-like) and somatosensory (unconditioned stimulus-like) stimuli (Bordi and LeDoux 1992; Romanski et al 1993). Further, during conditioning, the shortest latency conditioned unit responses occur in the dorsal subnucleus, and somewhat longer latency conditioned responses in the more ventral areas, including the medial subnucleus (Quirk et al 1995). Response latencies are longer in the central nucleus than in both of these areas (Pascoe and Kapp 1985). Detailed information about how the amygdala learns and stores information will require that the subnuclear organization be attended to.

But physiological recording studies are important for reasons other than their ability to pinpoint small areas of the amygdala. They are also crucial for understanding how the amygdala encodes experiences. Although the focus to date has been at the level of single units, it is clear that, as in other brain regions, information about how populations or ensembles encode information is going to be important. This level of analysis works in two ways. On the one hand, we need to understand how specific regions (like the dorsal subnucleus of the lateral nucleus) encode stimuli. On the other, we need to understand how pools of neurons in different regions interact during information processing (such as between areas of the auditory thalamus and subregions of the lateral nucleus, between subareas of the lateral nucleus, or between subareas of the lateral nucleus and subareas of other amygdala nuclei). The computing power for such analyses is now readily available and affordable. Analytic tools, though, need to be developed further to make the most use of the information that will be available with these techniques.

Mechanisms of Plasticity

Long-term potentiation (LTP) of synaptic transmission is high on many people's list as an explanation of how the brain learns and stores information (e.g., Bliss and Collingridge 1993; Nicoll and Malenka 1995). LTP has been studied most extensively in the hippocampus, but it has been very difficult to show that hippocampal LTP has anything to do with learning (Barnes 1995; Eichenbaum 1995). Over the past several years, we have taken a different approach. We started with the fact that thalamo-amygdala pathways are involved in fear learning, and have asked whether LTP occurs in these pathways. After finding evidence for LTP there (Clugnet and LeDoux 1990), we asked whether induction of LTP would affect the processing of a CS-like sound stimulus in this conditioning pathway (Rogan and LeDoux 1995). After finding that the processing of a sound by the amygdala was amplified by induction of LTP, we showed that fear conditioning did the same thing to the sound as LTP induction (Rogan et al 1997). This latter study and another one published at the same time (McKernan and Shinnick-Gallagher 1997) constitute the best evidence to date that LTP has anything to do with learning (Malenka and Nicoll 1997; Stevens 1998).

Because LTP is understood in such detail in the hippocampus, all the way to the level of molecules, it may be possible to apply some of this knowledge in the effort to understand the mechanisms of fear learning. In the best studied form of hippocampal LTP, the induction of plasticity involves the entry of calcium into the postsynaptic cell and activation of the *N*- methyl-D-aspartate (NMDA) class of glutamate receptors (see Bliss and Collingridge 1993; Nicoll and Malenka 1995). The maintenance of the plasticity then requires a cascade of intracellular events that include the cyclic adenosine monophosphate signaling system, protein and RNA synthesis, and gene action (see Huang et al 1996). The specific genes involved, though, are not known. That some of these mechanisms may apply to fear conditioning is suggested by studies that have manipulated NMDA receptors in the amygdala during learning (see Miserendino et al 1990; Maren and Fanselow 1996; Rogan and LeDoux 1996; Rogan et al 1997), and that have examined genetically altered mice that lack various components of intracellular cascades (Bourtchuladze et al 1994; Mayford et al 1996). Relatively little is known at this point about the molecular machinery of fear learning, and this is likely to be an important area for future research, especially given that it may open up new opportunities for drug therapy for fear and anxiety.

Role of the Human Amygdala

It has been known for some time that the primate temporal lobe (Kluver and Bucy 1937) and especially the amgydala (Weiskrantz 1956) is involved in fear and perhaps other emotional processes (Mishkin and Aggleton 1981; Aggleton 1992; Ono and Nishijo 1992; Rolls 1992); however, recent studies of humans with temporal lobe lesions that include (LaBar et al 1995) or are restricted mainly to the amygdala (Bechara 1995) have shown deficits in fear conditioning. The perception of fear in facial expressions (Young et al 1995; Adolphs et al 1994; but see Hamann et al 1996) and voices (Scott et al 1997) is also impaired. In addition, functional imaging studies have now shown activation of the amygdala during fear conditioning (LaBar et al 1998; Buchel et al 1998) and while processing faces and other emotional stimuli (Breiter et al 1996; Morris et al 1996). It thus seems clear that the animal data apply to the human brain. Future studies of the human amygdala will be required to determine how, if at all, the amygdala contributes to the subjective experience of emotions such as fear. Speculations on this topic can be found in LeDoux (1996) and Damasio (1994).

From Reaction to Action and Feeling

Essentially all of the recent work on the amygdala and fear has concentrated on the reactions that are automatically elicited in threatening situations. But clearly there is more to understand. Automatic, evolutionarily programmed responses to danger are typically followed by willful actions. We startle and freeze, and then decide to run away or stay put. Little is known about the manner in which the transition from emotional reaction to emotional action occurs, but some evidence suggests that interactions between the amygdala and corticostriatal motor systems are important (Everitt and Robbins 1992; LeDoux 1996). As little as we know about voluntary emotional actions, we know even less about conscious emotional feelings. It seems to me, though, that to the extent that working memory is a staging area for consciousness (Baars 1988; Kosslyn and Koenig 1992; Kihlstrom 1987), then feelings may result from the representation in working memory that an emotion system, like the fear system, is active. At a minimum, this suggestion provides a research strategy for studying feelings.

What about Other Emotions?

The neural basis of emotions other than fear is not clearly understood. Part of the difficulty is that there are not, at this point, good tasks for studying other emotions. Evidence that amygdala damage produces some deficit on some task that has some emotional relevance needs to be cautiously interpreted. The reason we can say so much about fear and fear disorders from studies of the neural basis of fear is because we have a great deal of information about how fear is organized in the brain. Until that level of

information is available about other emotions, it will not be easy to extrapolate from isolated findings about the effects of lesions to an understanding of how this or that emotion is mediated by the brain.

Conclusions

We have come a long way in our understanding of the amygdala and its contribution to fear and fear learning. As a result, fear is the emotion that is best understood in terms of brain mechanisms. Although some controversies have arisen, these reflect the normal checks and balances of the scientific enterprise, and in no way detract from the fundamental fact that the amygdala is the heart and soul of the fear system. New findings, pouring in all the time, are adding to this powerful database and will hopefully set the stage for a neurobiological understanding not only of the way the fear system normally works, but also of how it breaks down in anxiety disorders.

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