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The amygdala: vigilance and emotion

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Here we provide a review of the animal and human literature concerning the role of the amygdala in fear conditioning, considering its potential influence over autonomic and hormonal changes, motor behavior and attentional processes. A stimulus that predicts an aversive outcome will change neural transmission in the amygdala to produce the somatic, autonomic and endocrine signs of fear, as well as increased attention to that stimulus. It is now clear that the amygdala is also involved in learning about positively valenced stimuli as well as spatial and motor learning and this review strives to integrate this additional information. A review of available studies examining the human amygdala covers both lesion and electrical stimulation studies as well as the most recent functional neuroimaging studies. Where appropriate, we attempt to integrate basic information on normal amygdala function with our current understanding of psychiatric disorders, including pathological anxiety. *Molecular Psychiatry* (2001) **6,** 13–34.

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The amygdala

The term amygdala (Latin for almond) was first used in 1819 by the anatomist Burdach to describe an almond-shaped cell mass located deep in the human temporal cortex and is now used to describe a similar area in many species. As originally described, the amygdala is composed of several distinct groups of cells, usually termed the lateral, basal and accessory basal nuclei, and now collectively termed the basolateral amygdala. Several structures surrounding the basolateral amygdala, including the central, medial and cortical nuclei, are traditionally included in the 'amygdaloid complex'. These surrounding structures, together with the basolateral amygdala, have come to be called 'the amygdala'.

The extended amygdala

It is now clear that the basolateral amygdala is involved in negative and positive affect as well as spatial and motor learning. Moreover, including the basolateral nucleus with certain surrounding nuclei such as the central, medial, and cortical nuclei, into a single entity does not make anatomical sense. These neighboring structures are vastly different from the basolateral amygdala. In fact, in terms of cell shape, cell content and projection patterns, they are more similar to each other and other targets of the basolateral amygdala than they are to the basolateral amygdala itself. For example, the central nucleus of the amygdala (CeA), together with its rostral extension (lateral bed nucleus of stria terminalis), is organized on very similar lines to the dorsally situated striatopallidum. The cortical nuclei have strong olfactory relations and resemble adjacent olfactory cortical structures.

Thus, it is more useful to think of the amygdala as the 'basolateral amygdala' and to think of its several target areas as parts of a broader network that subserve more specialized functions (Figure 1 in Reference 1).[1] The basolateral amygdala receives sensory information from the thalamus, hippocampus and cortex and then activates or modulates synaptic transmission in target areas appropriate for the reinforcement signal with which the sensory information has been associated. A light paired with food can serve as a positive reinforcer by changing neural transmission in the basolateral amygdala which sends signals to the striatum, leading to approach behavior. Outputs to the CeA are important for paying more attention to a stimulus paired with food.[2] A light paired with shock may change neural transmission in the basolateral amygdala which projects to the CeA to produce the somatic, autonomic and endocrine signs of fear, as well as increased attention to that stimulus. These conditioned effects often depend on *N*-methyl-D-aspartate receptor activation within the basolateral amygdala when initially neutral stimuli, such as lights or tones, are paired with emotionally significant stimuli, such as shocks or food.[3,4] More long-lasting fear-like effects, not necessarily dependent on conditioning, may involve outputs to the lateral bed nucleus of the stria terminalis (BNST) and may be more akin to anxiety than fear.[5] Outputs

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to the striatum also may be involved in avoidance of stimuli paired with aversive events. Outputs to the hippocampus may influence the development of conscious memories of emotional events as well as modulating spatial learning. Finally, reciprocal connections with cortical areas may be involved in the representations of these positive or negative rewards in memory to guide appropriate choice behavior. Because most of the literature on the amygdala has analyzed the role of the basolateral amygdala and its adjacent target, the CeA, in aversive conditioning, this work will serve as the main focus of the present review. Brief summaries of the role of basolateral amygdala outputs to other targets shown in Figure 1 will follow.

The basolateral amygdala to CeA or BNST pathway as it relates to conditioned and unconditioned fear

The lateral and basolateral nuclei of the amygdala receive highly processed sensory information (for a highly comprehensive review in rats, monkeys and cats see McDonald).[6] In turn, these nuclei project to the CeA which then projects in part to hypothalamic and brainstem target areas that directly mediate specific signs of fear and anxiety. A great deal of evidence now indicates that the basolateral amygdala to CeA connection along with the efferent projections of the CeA collectively represent a central fear system involved in both the expression and acquisition of conditioned fear.[7–14] Figure 2 summarizes work done in many different laboratories indicating that the CeA has direct projections to a variety of anatomical areas that might be expected to be involved in many of the symptoms of fear or anxiety. This work has recently been reviewed where a full list of references can be found.[15]

Most of the literature on the amygdala involves an analysis of the role of the CeA using various measures of fear, primarily in rodents. Techniques have included mechanical and chemical lesions, electrical stimulation and local infusion of various compounds. A major caveat that needs to be kept in mind is that many effects attributed to the CeA may actually result from disconnecting the basolateral nucleus from the BNST because the fibers that connect the Bla to the BNST pass right through the CeA. This is illustrated in Figure 3 prepared by Dr Changjun Shi in which an anterograde tracer was infused into the posterior part of the basolateral nucleus of the amygdala and the brain was later sectioned so as to capture labeled terminals in both the CeA and the BNST. Many fibers synapse in the CeA but many pass through the CeA to terminate in the BNST. Hence, electrical stimulation or mechanical lesions of the CeA not only disrupt cells in the CeA, but also disconnect the basolateral nucleus from the BNST. Furthermore, the posterolateral division of the BNST has many of the same hypothalamic and brainstem projections as the CeA so that outputs from the basolateral nucleus of the amygdala to the BNST can eventually activate the same targets as the CeA does.

In addition, the CeA projects heavily to the lateral division of the BNST that collectively is known as the *lateral extended amygdala*.[16] Thus, electrical or chemical stimulation of the CeA not only can activate CeA cells that project to the hypothalamus and brainstem but also CeA cells that project to the BNST. Similarly, chemical, fiber-sparing lesions of the CeA also can block inputs from the CeA to the BNST. Hence, manipulations of the CeA potentially will always have these dual effects on the CeA and the BNST. Because of this, the present review will conclude a role for either the CeA or BNST based on manipulations of the CeA.

Autonomic and hormonal measures of fear related to CeA/BNST projections

Anatomically, the CeA and the BNST are well situated to mediate the various components of the fear response. Both structures send prominent projections to areas such as the lateral hypothalamus which is involved in activation of the sympathetic autonomic nervous system seen during fear and anxiety.[17] Direct projections to the dorsal motor nucleus of the vagus, nucleus of the solitary tract and ventrolateral medulla

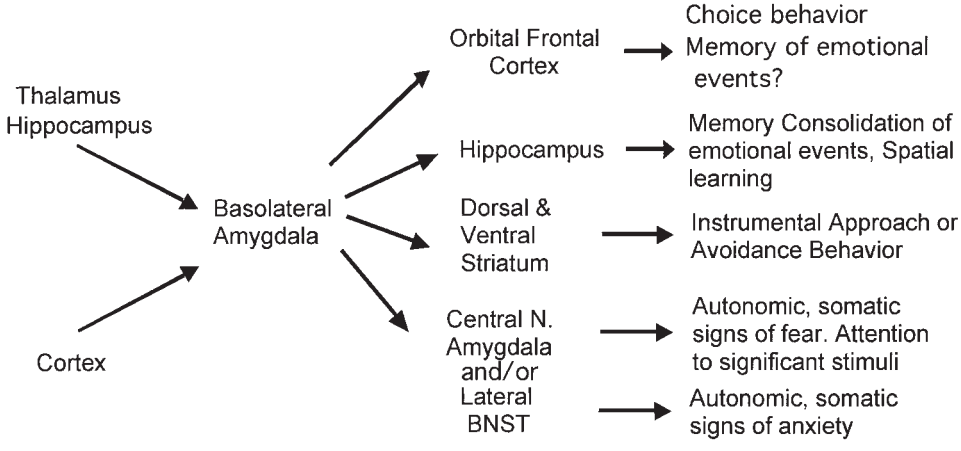

Figure 1 Schematic diagram of the outputs of the basolateral nucleus of the amygdala to various target structures and possible functions of these connections.

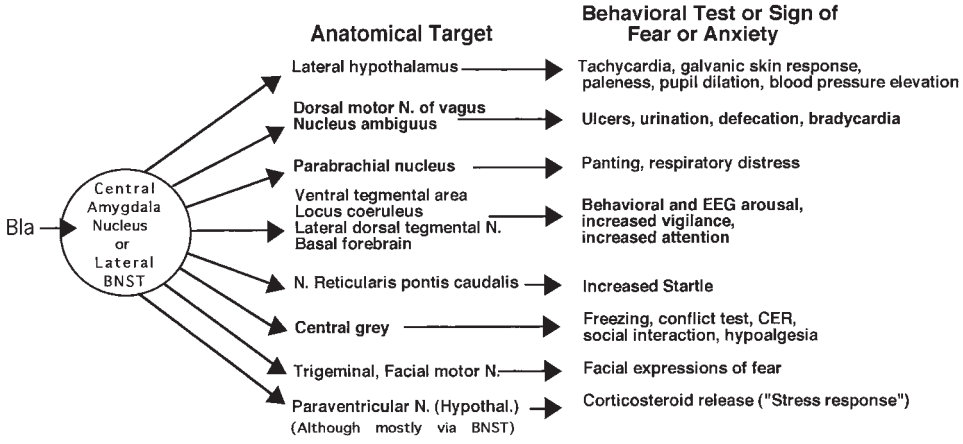

Figure 2 Schematic diagram of the outputs of the central nucleus or the lateral division of the bed nucleus of the stria terminalis (BNST) to various target structures and possible functions of these connections.

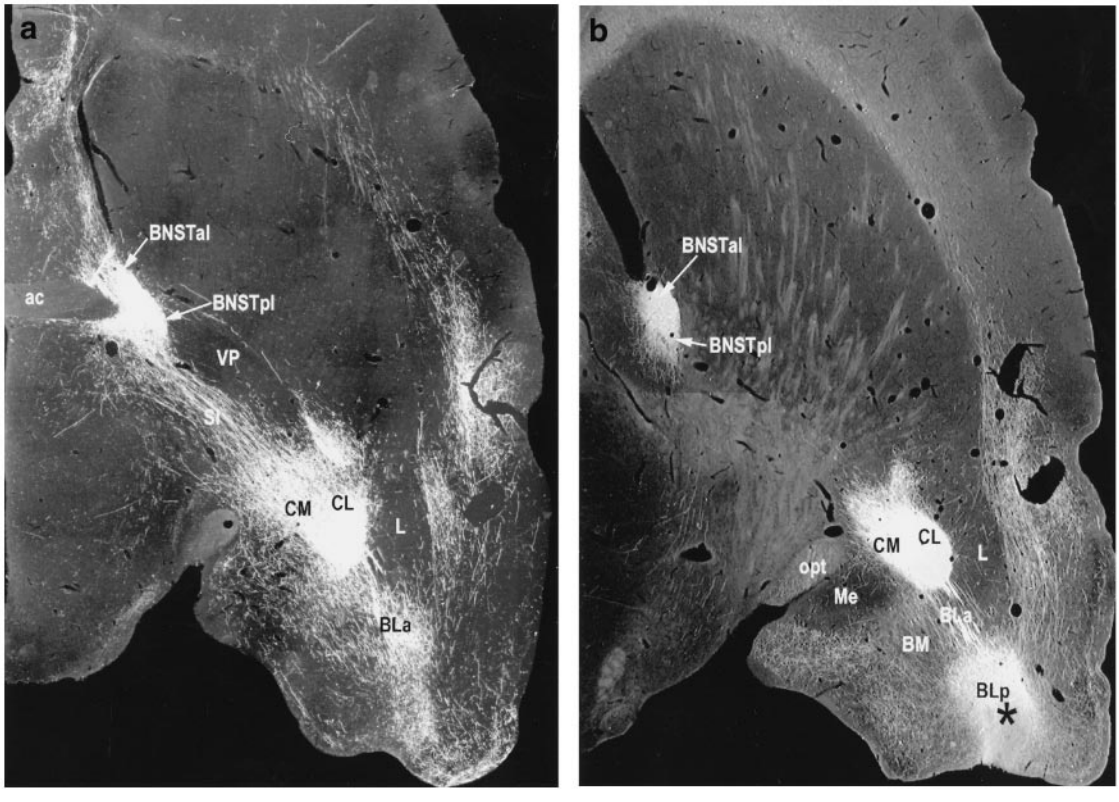

Figure 3 Photomicrographs of a horizontal section of the rat brain showing a deposit of biotinylated dextran amine (BDA) into the posterior basolateral nucleus of the amygdala (BLp). Panel (a) shows horizontal section more ventral than that shown in panel (b). Note that fibers originating from cells in the BLp stream through the more anterior part of the basolateral amygdala (Bla) to terminate in the medial (CM) and lateral (CL) divisions of the central nucleus of the amygdala. However, other fibers pass directly through the central nucleus on route to the anterior (BNSTal) and posterior (BNSTpl) regions of the lateral bed nucleus of the stria terminalis. Thus electrolytic lesions of the central nucleus of the amygdala would not only disrupt the function of the central nucleus but also disrupt input from the basolateral amygdala to the BNST. BDA was deposited via iontophoresis using a 5% solution in phosphate-buffered saline at a current of 4 μA over 10 min. The brain was blocked in such a way as to capture the amygdala and the more dorsally located bed nucleus of the stria terminalis in the same 30-μm section. Other abbreviations: ac, anterior commissure; BM, basomedial nucleus of the amygdala; L, lateral nucleus of the amygdala; ME, medial nucleus of the amygdala; opt, optic tract; SI, substantia innominata; VP, ventral pallidum. This very difficult procedure was carried out by Dr Changjun Shi who graciously allowed us to include this figure.

may be involved in lateral extended amygdala modulation of heart rate and blood pressure which are known to be regulated by these brainstem nuclei.[18] Projections to the parabrachial nucleus may be involved in respiratory (as well as cardiovascular changes) during fear, because electrical stimulation or lesions of this nucleus are known to alter various measures of respiration. Indirect projections of the CeA to the paraventricular nucleus via the BNST and preoptic area may mediate the prominent neuroendocrine responses to fearful or stressful stimuli.

Attention and vigilance related to CeA/BNST projections

Projections from the CeA or BNST to the ventral tegmental area may mediate stress-induced increases in dopamine metabolites in the prefrontal cortex.[19] Direct projections to the dendritic field of the locus coeruleus or indirect projections via the paragigantocellularis nucleus may mediate the response of cells in the locus coeruleus to conditioned fear stimuli as well as being linked to fear and anxiety.[20,21] Direct projections to the lateral dorsal tegmental nucleus and parabrachial nuclei, which have cholinergic neurons that project to the thalamus, may mediate increases in synaptic transmission in thalamic sensory relay neurons during states of fear. This cholinergic activation, along with increases in thalamic transmission accompanying activation of the locus coeruleus, may thus lead to increased vigilance and superior signal detection in a state of fear or anxiety.

As emphasized by Kapp *et al*,[22] in addition to its direct connections to the hypothalamus and brainstem, the CeA also has the potential for indirect widespread effects on the cortex via its projections to cholinergic neurons that project to the cortex. In fact, the rapid development of conditioned bradycardia during Pavlovian aversive conditioning, critically dependent on the amygdala, may not be simply a marker of an emotional state of fear, but instead a more general process reflecting an increase in attention. In the rabbit, low voltage, fast EEG activity, generally considered a state of cortical readiness for processing sensory information, is acquired during Pavlovian aversive conditioning at the same rate as conditioned bradycardia.

Fear-induced changes in motor behavior related to CeA/BNST projections

Release of norepinephrine onto motor neurons via lateral extended amygdala activation of the locus coeruleus, or via projections to serotonin containing raphe neurons, could lead to enhanced motor performance during a state of fear, because both norepinephrine and serotonin facilitate excitation of motor neurons.[23,24] Direct projections to the nucleus reticularis pontis caudalis, as well as indirect projections to this nucleus via the central gray probably are involved in fear-potentiation of the startle reflex. Direct projections to the lateral tegmental field, including parts of the trigeminal and facial motor nuclei, may mediate some of the facial expressions of fear as well as potentiation of the eyeblink reflex. The lateral extended amygdala also projects to regions of the central gray that appear to be a critical part of a general defense system and which have been implicated in conditioned fear in a number of behavioral tests including freezing, sonic and ultrasonic vocalization and stress-induced hypoalgesia.[17,25–29]

Elicitation of fear responses by electrical or chemical stimulation of the extended amygdala

Electrical stimulation or abnormal electrical activation of the amygdala (ie, via temporal lobe seizures) can produce a complex pattern of behavioral and autonomic changes that, taken together, highly resemble a state of fear. This probably results from simultaneous activation of many of the target areas seen in Figures 1 and 2 during focal stimulation of the amygdala. In fact, we have recently found in waking, alert rats, that low level electrical stimulation of the CeA leads to an increase in c-fos protein, a marker of neuronal activation, of many of these target areas in the same animal (Shi and Davis, unpublished observations).

Autonomic and hormonal measures

As outlined by Gloor[30] 'The most common affect produced by temporal lobe epileptic discharge is fear . . . It arises 'out of the blue.' Ictal fear may range from mild anxiety to intense terror. It is frequently, but not invariably, associated with a rising epigastric sensation, palpitation, mydriasis, and pallor and may be associated with a fearful hallucination, a frightful memory flashback, or both' (p 513). In humans, electrical stimulation of the amygdala elicits feelings of fear or anxiety as well as autonomic reactions indicative of fear.[31,32] While other emotional reactions occasionally are produced, the major reaction is one of fear or apprehension. However, it is not clear whether these effects result from activation of the CeA or more widespread effects to other parts of the extended amygdala.

Electrical stimulation of the CeA or chemical activation via the cholinergic agonist carbachol or the neurotransmitter glutamate produces prominent cardiovascular effects that depend on the species, site of stimulation and state of the animal. CeA stimulation can also produce gastric ulceration and increase gastric acid, which can be associated with chronic fear or anxiety. It can also alter respiration, a prominent symptom of fear, especially in panic disorder.

Using very small infusion cannulas, Sanders and Shekhar[33] found increases in blood pressure and heart rate when the GABA-A antagonist bicuculline was infused into the basolateral but not the central nucleus. Local infusion of NMDA or AMPA into the basolateral nucleus also increased blood pressure and heart rate.[34] These effects, as well as those of bicuculline, could be blocked by local infusion of either NMDA or non-NMDA antagonists into the amygdala[34,35] or the dorsomedial hypothalamus.[36]

Repeated infusion of initially subthreshold doses of bicuculline into the anterior basolateral nucleus led to

a 'priming' effect in which increases in heart rate and blood pressure were observed after 3–5 infusions.[37] This change in threshold lasted at least 6 weeks and could not be ascribed to mechanical damage or generalized seizure activity based on EEG measurements. Similar changes in excitability were produced by repetitive infusion of very low doses of corticotropin releasing hormone (CRH) or urocortin.[38] Once primed, these animals exhibited behavioral and cardiovascular responses to intravenous sodium lactate, a panic-inducing treatment in certain types of psychiatric patients. It is possible, therefore, that long-term stress or prior trauma could lead to similar priming effects that would make the amygdala, or structures to which it connects, more reactive to subsequent stressors, thereby leading to certain types of psychiatric disorders.

Alternatively, genetic differences in GABA or CRH tone in the amygdala could render individuals hyperresponsive to stress or anxiety (see excellent recent reviews by Adamec[39] and Rosen and Schulkin[40] for more on this idea).

In general, electrical stimulation of the amygdala causes an increase in plasma levels of corticosterone. The effect of electrical stimulation appears to depend on both norepinephrine and serotonin in the paraventricular nucleus. Depletion of these transmitters via local infusions of 6-OHDA or 5,7-DHT, or local infusion of the norepinephrine or serotonin antagonists prazosin or ketanserin, in the paraventricular nucleus attenuated the effects of electrical stimulation.[41]

Attention and vigilance

Studies in several species indicate that electrical stimulation of the CeA increases attention or processes associated with increased attention. For example, stimulation of sites in the CeA that produce bradycardia[12] also produce low voltage fast EEG activity in both rabbits[42] and rats.[43] In fact, an attention or orienting reflex was the most common response elicited by electrical stimulation of the amygdala.[44,45] These and other observations have led Kapp *et al*[22] to hypothesize that the 'CeA and its associated structures function, at least in part, in the acquisition of an increased state of nonspecific attention or arousal manifested in a variety of CRs which function to enhance sensory processing. This mechanism is rapidly acquired, perhaps via an inherent plasticity within the nucleus and associated structures in situations of uncertainty but of potential import; for example, when a neutral stimulus (CS) precedes either a positive or negative reinforcing, unexpected event (US)' (p 241). Electrical stimulation of the amygdala can also activate cholinergic cells that are involved in arousal-like effects depending on the state of sleep and perhaps the species.

Motor behavior

Electrical or chemical stimulation of the CeA produces a cessation of ongoing behavior, a critical component in several animal models such as freezing, the operant conflict test, the conditioned emotional response, and the social interaction test. Electrical stimulation of the amygdala also elicits jaw movements and activation of facial motoneurons, which probably mediate some of the facial expressions seen during the fear reaction. These motor effects may be indicative of a more general effect of amygdala stimulation, namely that of modulating brainstem reflexes such as the massenteric, baroreceptor nictitating membrane, eyeblink and the startle reflex.

Summary of the effects of stimulation of the amygdala

Viewed in this way, the pattern of behaviors seen during fear may result from activation of a single area of the brain (the extended amygdala), which then projects to a variety of target areas, each of which are critical for the specific symptoms of fear (the expression of fear), as well, perhaps, for the experience of fear. Moreover, it must be assumed that these connections are already formed in an adult organism, because electrical stimulation produces these effects in the absence of prior explicit fear conditioning. Thus, much of the complex behavioral pattern seen during a state of 'conditioned fear' has already been 'hard wired' during evolution. For a formerly neutral stimulus to produce the constellation of behavioral effects used to define a state of fear or anxiety, it is only necessary for that stimulus to activate the amygdala following aversive conditioning. In turn this will produce the complex pattern of behavioral changes by virtue of the innate connections between the amygdala and these different brain target sites. Hence, plasticity during fear conditioning probably results from a change in synaptic inputs prior to or in the basolateral amygdala,[46–48] rather than from a change in its efferent target areas. The ability to produce LTP in the basolateral amygdala[49–54] that can lead to an increase in responsiveness to a physiological stimulus,[55] and the finding that local infusion of NMDA antagonists into the amygdala block the acquisition of fear conditioning[15] are consistent with this hypothesis.

Effects of lesions of the amygdala on conditioned fear

The Kluver–Bucy syndrome

In 1939, following earlier work, Kluver and Bucy[56] described the now classic behavioral syndrome of monkeys with bilateral removal of the temporal lobes including the amygdala, hippocampus and surrounding cortical areas. Following such lesions the monkeys developed 'psychic blindness' where they would approach animate and inanimate objects without hesitation and examine these objects by mouth rather than by hand, be they a piece of food, feces, a snake or a light bulb. They also had a strong tendency, almost a compulsion, to attend to and examine every visual stimulus that came into their field of view and showed a marked change in emotional behavior. These monkeys had a striking absence of emotional motor and vocal reactions normally associated with stimuli or

situations eliciting fear and anger. As described by Kluver and Bucy, 'The typical reaction of a 'wild' monkey when suddenly turned loose in a room consists in getting away from the experimenter as rapidly as possible. It will try to find a secure place near the ceiling or hide in an inaccessible corner where it cannot be seen. If seen, it will either crouch and, without uttering a sound, remain in a state of almost complete immobility or suddenly dash away to an apparently safer place. This behavior is frequently accompanied by other signs of strong emotional excitement. In general, all such reactions are absent in the bilateral temporal monkey. Instead of trying to escape, it will contact and examine one object after another or other parts of the objects, including the experimenter, stranger or other animals ... Expressions of emotions, such a vocal behavior, 'chattering' and different facial expressions, are generally lost for several months. In some cases, the loss of fear and anger is complete' (p 991). Finally, many monkeys showed striking increases in heterosexual and homosexual behavior never previously observed in this monkey colony.

Lesions of the temporal lobe also were reported to cause profound changes in social behavior of monkeys both in the laboratory and the wild. Following temporal lobe lesions, monkeys rapidly fell in rank within dominance hierarchies established in monkey colonies (for review see Kling and Brothers).[57] Lesioned monkeys now tried to fight with more dominant, larger monkeys, leading to frequent and often severe wounds. In the wild, these inappropriate interactions with other monkeys led to repeated attacks, social isolation and eventual death.[58,59]

Subsequent studies have shown that all of the emotional components of the Kluver–Bucy syndrome can be reproduced by removal of the amygdala and surrounding perirhinal and entorhinal cortex.[60–65] The tameness and excessive orality can be reproduced by lesions restricted to only the amygdala.[66] Zola-Morgan *et al*[67] found that lesions of the amygdala disrupted emotional behavior to a set of novel objects whereas lesions of the hippocampus or surrounding cortical areas, did not. Conversely, damage to the hippocampus and the anatomically related perirhinal and parahippocampal cortex impaired memory but not emotional behavior. Moreover, combined damage to the amygdala and hippocampus had no greater effect on memory or emotion than damage to either structure alone.

Although the Kluver–Bucy syndrome has been enormously important for focussing attention onto the amygdala, more recent studies using techniques that selectively destroy amygdala neurons rather than ones that destroy both cells and fibers that pass through the amygdala have had much more subtle effects. For example, ibotenic-induced lesions of even relatively large parts of the amygdala do not reproduce the Kluver–Bucy syndrome in rhesus monkeys. However, these animals appear less fearful of snakes because they will reach for an object next to a toy snake at a shorter latency than non-lesioned monkeys.[68] Moreover, these animals appear to be less weary and less vigilant because other, non-lesioned, monkeys are more apt to brush up against the lesioned monkeys and mount and play with them (Kalin, personal communication).

Humans only rarely show the full-blown Kluver–Bucy syndrome following lesions restricted to the amygdala, although they consistently show a blunting of emotional reactivity. This finding, along with the frequent change in emotional behaviors seen in Alzheimer's disease, and other neurological diseases associated with amygdala pathology, is further evidence for the role of the amygdala in human emotion.[69,70] It is not surprising, therefore, that several authors have seen a connection between the social inappropriateness following temporal lobe damage in monkeys and some of the negative or deficit symptoms in schizophrenia. These include inappropriate mood, flat affect, social isolation, poverty of speech and difficulty in identifying the emotional status of other people.[69,71]

Face recognition and classical fear conditioning in humans

In non-human primates[72–74] and humans,[75,76] cells have been found that respond selectively to faces or direction of gaze.[77] In humans, removal of the amygdala has been associated with an impairment of memory for faces[78–81] and deficits in recognition of emotion in people's faces and interpretation of gaze angle.[81,82,292] In a very rare case involving bilateral calcification confined to the amygdala (Urbach–Wiethe disease), Patient SM046 could not identify the emotion of fear in pictures of human faces. Moreover, she could not draw a fearful face, even though other emotions such as happy, sad, angry and disgusted were identified and drawn within the normal range. Furthermore, she had no difficulty in identifying the names of familiar faces.[83,84] Based on these and other data, Adolphs *et al*[84] proposed that 'the amygdala is required to link visual representation of facial expression, on the one hand, with representation that constitute the concept of fear, on the other' (p 5879). This patient and two others also tended to view even the most threatening faces as trustworthy and approachable.[85]

A more detailed evaluation of patient SM046 showed that she correctly identified valence (eg pleasant *vs* unpleasant) in faces displaying happy, surprised, afraid, angry, disgusted, or sad emotion but was highly abnormal in rating the level of arousal to the afraid, angry, disgusted and sad faces.[86] Interestingly, her arousal ratings for the happy and surprised faces were in the normal range. She also had a very similar pattern when judging the valence or arousal of sentences and words. The authors suggest these deficits may reflect a blockade of acquisition rather than retrieval of knowledge about the arousing aspects of negative emotions because patients who sustained amygdala damage late in life showed normal recognition of fear in human faces.[87] In contrast, SMO46's lesion occurred very early in life, perhaps at birth. In fact, a deficit in arousal could explain a decrease in fear acquisition because patients with long-standing bilateral amygdala damage

failed to show the normal enhancement in memory for emotional material.[88–90] This is known from preclinical studies to be dependent on activation of B-noradrenergic receptors in the amygdala[91] as a result of arousal-induced activation of noradrenergic-containing cells.

Another patient (SP) with extensive bilateral amygdala damage also showed a major deficit in her ability to rate levels of fear in human faces, yet was perfectly normal in generating a fearful facial expression in comparison to normal subjects, based on the ratings of three judges.[92] Moreover, she also had preserved evaluation of vocal expressions of fear[93] and patient SM046 had no deficit in judging the emotional quality of music.[94] These data suggest the amygdala lesions in these patients affected the ability to process the social signals of fear rather than altering the experience or feeling of fear.

Autonomic and hormonal measures

Patients with unilateral[95] or bilateral[96] lesions of the amygdala also have been reported to have deficits in classical fear conditioning using the galvanic skin response as a measure. In monkeys, removal of the amygdala decreases reactivity to sensory stimuli measured with the galvanic skin response.[97,98] In rodents lesions of the amygdala block conditioned changes in heart rate and blood pressure. Ablation of the amygdala can reduce the secretion of ACTH or corticosteroids as well as reducing stress-induced increases in dopamine release in the frontal cortex. Lesions of the CeA have been found to significantly attenuate ulceration produced by restraint or shock stress or elevated levels of plasma corticosterone produced by restraint stress. Lesions of the amygdala have been reported to block the ability of high levels of noise, which may be an unconditioned fear stimulus, to produce hypertension,

Motor behavior

Numerous studies have shown that lesions of the amygdala eliminate or attenuate conditioned freezing normally seen in response to a stimulus formerly paired with shock (cf Ref 15). Lesions of the amygdala counteract the normal reduction of bar pressing or licking in the operant conflict test and the conditioned emotional response paradigms. They also can block high-frequency vocalizations as well as reflex facilitation such as fear-potentiated startle. Lesions of the amygdala also produce a dramatic decrease in shock-probe avoidance.

Lesions of the amygdala are known to block several measures of innate fear in different species.[99,100] Lesions of the cortical amygdaloid nucleus and perhaps the central nucleus markedly reduce emotionality in wild rats measured in terms of flight and defensive behaviors. Large amygdala lesions dramatically increase the number of contacts a rat will make with a sedated cat.[99] In fact, some of these lesioned animals crawl all over the cat and even nibble its ear, a behavior never shown by the non-lesioned animals. Following lesions of the archistriatum birds become docile and show little tendency to escape from humans, consistent with a general taming effect of amygdala lesions reported in many species[101] and perhaps related to the increase in trust following lesions in humans (see above). Recently, patients who underwent bilateral amygdalotomy for intractable aggression showed a reduction in autonomic arousal levels to stressful stimuli and in the number of aggressive outbursts, although they continued to have difficulty controlling aggression.[102]

This, along with a large literature implicating the amygdala in many other measures of fear such as active and passive avoidance[14,91,100,103–105] and evaluation and memory of emotionally significant sensory stimuli,[91,106–118] provides strong evidence for a crucial role of the amygdala in fear.

Attention and vigilance

Because the CeA is so important for the expression of fear conditioning its role in attention is difficult to evaluate using a lesion approach and measuring fear conditioning. However, using an appetitive procedure, Michela Gallagher and Peter Holland have found results consistent with an attentional role of the CeA. In these studies,[119] a CS such as a light or a tone is paired with receipt of food. Initially rats rear when the light goes on or show small orienting responses when the tone goes on, both of which habituate with stimulus repetition. When these stimuli are then paired with food, these initial orienting responses return (CS-generated CRs) along with approach behavior to the food cup (US-generated responses). Neurotoxic lesions of the CeA severely impair CS-generated responses without having any effect on unconditioned orienting responses or US-generated responses. Based on these data, the authors conclude that the CeA modulates attention to a stimulus that signals a change in reinforcement. Further work seemed to confirm this hypothesis. For example, rats with lesions of the central nucleus fail to benefit from procedures that normally facilitate attention to conditioned stimuli.[120,121]

Differential roles of the central and basolateral nuclei have been found in a phenomenon known as taste-potentiated odor aversion learning. In this test, which requires processing information in two sensory modalities, rats develop aversions to a novel odor paired with illness only when the odor is presented in compound with a distinctive gustatory stimulus. Electrolytic[122] or chemical lesions[123] of the basolateral but not the CeA blocked taste-potentiated odor aversion learning even though they had no effect on taste aversion learning itself. Depletion of dopamine and norepinephrine in the amygdala via local infusion of 6-hydroxydopamine also blocked odor aversion but not taste aversion.[124] Local infusion of NMDA antagonists into the basolateral nucleus also blocked the acquisition but not the expression of taste-potentiated odor aversion but had no effect on taste aversion learning itself.[125] Based on these and other data, Hatfield *et al*[126] suggest their data support the view that the CeA 'regulates attentional processing of cues during associative con-

ditioning' (p 5265),[126] whereas the basolateral nucleus of the amygdala is critically involved in 'associative learning processes that give conditioned stimuli access to the motivation value of their associated unconditioned stimuli' (p 5264).[126]

A role for the amygdala in attention also has been implicated in studies that recorded stimulus-evoked electrical activity in the amygdala in epileptic patients.[127] In these studies subjects were presented with a series of visual or auditory stimuli, some of which they were instructed to ignore and others to attend. Averaged evoked responses showed a prominent negative-positive component occuring roughly 200–300 ms after stimulus onset (N200/P300). These components, especially N200, were prominent within the amygdala and much larger when elicited by a stimulus to which the subject was asked to attend. Halgren summarizes the cognitive conditions that evoke the N200/P300 as being stimuli that are novel or signals for behavioral tasks and hence necessary to attend and process. Moreover, these components, along with other autonomic measures of the orienting reflex, seem to form an overall reaction of humans to stimuli that demand their evaluation.

Effects of local infusion of drugs into the amygdala on measures of fear and anxiety

Figure 2 suggests that spontaneous activation of the amygdala would produce a state resembling fear or anxiety in the absence of any obvious eliciting stimulus. In fact, fear and anxiety often precede temporal lobe epileptic seizures[30,32] which are usually associated with abnormal electrical activity of the amygdala.[128] If the amygdala is critically involved in fear and anxiety, then drugs that reduce fear or anxiety clinically may well act within the amygdala. It is also probable that certain neurotransmitters within the amygdala especially may be involved in fear and anxiety. For example, the amygdala has a high density of CRH receptors[129] and CRH nerve endings[130] and several recent papers indicate that stress, as well as conditioned fear, can induce a release of CRH in the amygdala which results in various anxiogenic effects. In fact, a large number of studies indicate that local infusion of GABA or GABA agonists, benzodiazepines, CRH antagonists, opiate agonists, neuropeptide Y, dopamine antagonists or glutamate antagonists decrease measures of fear and anxiety in several animal species. Table 1 gives selected examples of some of these studies. Conversely, local infusion of GABA antagonists, CRH or CRH analogues, vasopressin, TRH, opiate antagonists, CCK or CCK analogues tend to have anxiogenic effects. Table 2 shows selected examples of such studies, which, along with those in Table 1, are reviewed in Davis.[15]

In summary, connections between the basolateral amygdala and the central nucleus or the bed nucleus of the stria terminalis are critically involved in various autonomic and motor responses seen during a state of fear or anxiety. However, it is also the case that connections between the basolateral nucleus and other target areas are involved in emotional behavior (Figure 1).

The basolateral amygdala to ventral striatum pathway as it relates to emotion

Although a full description of the role of this pathway is beyond the scope of this paper, it is clear that projections from the amygdala to the ventral striatum are involved in certain forms of appetitive behavior and perhaps positive affect in general. The basolateral nucleus of the amygdala projects directly to the nucleus accumbens in the ventral striatum,[181] in close apposition to dopamine terminals of A10 cell bodies in the ventral tegmental area.[182] Morgenson and colleagues suggested that the ventral striatum was the site where affective processes in the limbic forebrain gained access to subcortical elements of the motor system that resulted in appetitive actions.[183] Local infusion into the nucleus accumbens of drugs such as d-amphetamine, which release dopamine, increase the magnitude of conditioned reinforcement in operant tasks, ie pressing a bar to turn on a light that previously was paired with food.[184] These facilitative effects can be blocked by local infusion of 6-OHDA[185] or glutamate antagonists such as CNQX or AP5.[186] However, 6-OHDA did not block the expression of conditioned reinforcement itself, suggesting that the reinforcement signal comes from some other brain area that projects to the nucleus accumbens. In fact, excitotoxic lesions of the basolateral amygdala significantly reduced bar pressing for the conditioned reinforcer but local infusion of d-amphetamine in these lesioned rats still facilitated performance, albeit at a lower baseline level or responding.[187] These results suggest that two relatively independent processes operate during conditioned reinforcement. First, information from the amygdala concerning the CS-US association is sent to the nucleus accumbens that leads to approach behavior to the conditioned reinforcer. Second, dopamine in the nucleus accumbens amplifies these signals from the amygdala. Perhaps similarly, acoustic startle amplitude is reduced when elicited in the presence of cues previously paired with food[188] and pre-training local infusion of 6-OHDA into the nucleus accumbens blocks this effect.[188] Connections between the basolateral amygdala and the ventral striatum also are involved in conditioned place preference.[189]

The basolateral amygdala to dorsal striatum pathway as it relates to conditioned and unconditioned fear

As emphasized by McGaugh, Packard, and others, the amygdala modulates memory in a variety of tasks such as inhibitory avoidance, motor or spatial learning.[104,190–193] For example, post-training intra-caudate injections of amphetamine enhanced memory in a visible platform water maze task but had no effect in the hidden platform, spatially guided task.[192,193] Conversely post-training intra-hippocampal infusion of

Table 1 Effects of local infusion into the amygdala of various neurotransmitter agonists on selected measures of fear and anxiety

Substance	*Species*	*Site*	*Effect of substance infused*	*Reference*
GABA or chlordiazepoxide	Rat	CeA	Decrease stress-induced gastric ulcers	131
GABA or Benzodiazepines	Rat	Bla	Increase punished responding in operant conflict test (Anticonflict effect)	132–136
Benzodiazepines	Rat	CeA	Increase punished responding in operant conflict test (Anticonflict effect)	137,138
Midazolam	Rat	Bla	More time on open arms in plus-maze (anxiolytic effect), no effect on shock probe avoidance	139
Diazepam	Rat	CeA or Bla	Decrease freezing to footshock	140,141
Diazepam	Mice	AC	More time in light side in light-dark box test (Anxiolytic effect)	142
Muscimol	Rat	Bla	Anxiolytic effect in the social interaction test. No effect in CeA	37
Muscimol	Rat	Bla	Increase punished responding in operant conflict test (Anticonflict effect). No effect in CeA	135
a-CRH	Rat	CeA	Block noise-elicited increase in tryptophan hydroxylase in cortex	143
a-CRH	Rat	CeA	Anxiolytic effect in plus maze in socially defeated rat	144
a-CRH	Rat	CeA	Anxiolytic effect in plus maze during ethanol withdrawal in ethanol-dependent rats. No effect in plus maze in non-dependent rats	145
a-CRH	Rat	CeA	Decrease behavioral effects of opiate withdrawal	146
CRH receptor antisense	Rat	CeA	Anxiolytic effect in plus maze in rats that previously experienced defeat stress	147
a-CRH	Rat	CeA	Decrease duration of freezing to an initial shock treatment or to re-exposure to shock box 24 h later	148
a-CRH	Rat	CeA	No effect on grooming and exploration activity under stress-free conditions	149
Enkephalin analog	Rat	CeA	Decrease stress-induced gastric ulcers, prevented by 6-OHDA or clozapine	150–152
Opiate agonists	Rb	CeA	Block acquisition of conditioned bradycardia	111,153
Morphine	Rat	CeA	Anxiolytic effect in social interaction test	154
Neuropeptide Y	Rat	Bla, not CeA	Anxiolytic effect in social interaction test, blocked by Y-1 antagonist	155
Neuropeptide Y1 agonist	Rat	CeA	Anxiolytic effects in conflict test. NPY-Y2 agonist much less potent	156
Oxytocin	Rat	CeA	Decrease stress-induced bradycardia and immobility responses	157
SCH 23390	Rat	AC	Decrease expression of fear-potentiated startle	158
SCH 23390	Rat	AC	Decrease acquisition and expression of freezing to tone or context. Not due to state-dependent learning	159
CNQX	Rat	Bla	Block expression of fear-potentiated startle (visual or auditory CS)	160
NBQX	Rat	Bla or CeA	Block expression of fear-potentiated startle (visual CS)	161
AP5	Rat	Bla	Block facilitation of eyeblink conditioning by prior stress when given prior to stressor session	162
AP5 or CNQX	Rat	Bla	Anxiolytic effect in social interaction test	163
CNQX	Rat	CeA	Decrease naloxone precipitated withdrawal signs in morphine-dependent rats	164

CeA, central nucleus of the amygdala; Bla, basolateral nuclei of the amygdala; AC, amygdaloid complex.

amphetamine enhanced memory in the hidden platform water maze task but not in the visible platform task. However, post-training intra-amygdala injections of amphetamine enhanced memory in both water maze tasks.[192,193] Moreover, pre-retention intra-hippocampal lidocaine injections blocked expression of the memory-enhancing effects of post-training intra-hippocampal amphetamine injections in the hidden platform task, and pre-retention intra-caudate lidocaine injections blocked expression of the memory-enhancing effects of

Table 2 Effects of local infusion into the amygdala of various neurotransmitter antagonists on selected measures of fear and anxiety

Substance	*Species*	*Site*	*Effect of substance infused*	*Reference*
Bicuculline, picrotoxin	Rat	Bla	Anxiogenic effect in the social interaction test. Repeated infusion led to sensitization	[37]
Bicuculline	Rat	Bla	Anxiogenic effects in social interaction, blocked by either NMDA or non-NMDA antagonists into the amygdala	[35]
Bicuculline (un)	Rat	Bla not CeA	Increases in blood pressure, heart rate and locomotor activity. Bigger effect with repeated infusions	[33,37]
Bicuculline (un)	Rat	Bla	Increases in blood pressure, heart rate. Blocked by infusion of either NMDA or non-NMDA antagonists into the amygdala	[35]
Bicuculline, NMDA, AMPA (un)	Rat	Bla	Increases in blood pressure, heart rate. Blocked by either NMDA or non-NMDA antagonists infused into Bla or the dorsomedial hypothalamus	[34,36]
CRH	Rat	CeA	Increase heart rate. Effect blocked by a-CRH into CeA	[165]
CRH, TRH or CGRP	Rat	CeA	Increase in blood pressure, heart rate and plasma catecholamines	[166]
Urocortin or CRH	Rat	Bla	After repeated subthreshold doses get increase in blood pressure to systemic lactate	[38]
CRH	Rat	CeA, not Bla	Increased grooming and exploration in animals tested under stress-free conditions (ie, in the home cage)	[149,167]
CRH	Rat	CeA	Increase defensive burying	[168]
CRH or Urocortin	Rat	Bla	Anxiogenic effect in plus maze, sensitization with repeated subthreshold doses. Now get behavioral and cardiovascular effects to systemic lactate	[38]
Vasopressin	Rat	CeA	Increased stress-induced bradycardia and immobility responses in rats bred for low rates of avoidance behavior but not the more aggressive rats that show high avoidance rates	[157]
Vasopressin	Rat	CeA	Bradycardia (low doses) or tachycardia and release of corticosterone (high dose). Tachycardia blocked by oxytocin antagonist	[169]
Vasopressin	Rat	CeA	Immobility, seizures second infusion	[170]
Vasopressin	Rat	CeA	Immobility in rats bred for low rates of avoidance but not bred for high avoidance rates	[157]
TRH	Rat	CeA	Increase stress-induced gastric ulcers	[150,152]
TRH or physostigmine	Rat	CeA	Increase stress-induced gastric ulcers, blocked by muscarinic or benzodiazepine agonists	[171]
TRH analogue	Rat	CeA	Increase gastric contractility, blocked by vagotomy	[172]
TRH	Rat	CeA	Produce gastric lesions and stimulated acid secretion	[173]
TRH analogue	Rat	AC	No effect on gastric secretion, whereas large effect after infusion into dorsal vagal complex or nucleus ambiguus	[174]
Naloxone	Rat	CeA	Increase stress-induced gastric ulcers	[150,152]
Naloxone	Rat	AC	Elicit certain signs of withdrawal (depending on site) in morphine-dependent rats (unilateral)	[175]
Methylnaloxonium	Rat	AC	Place aversion to context where injections given to morphine-dependent rats	[176]
Methylnaloxonium	Rat	AC	Weak withdrawal signs in morphine-dependent rats	[177]
Yohimbine	Rat	CeA	Facilitation of the startle reflex	[178]
CCK analogues	Rat	AC	Anxiogenic effect in plus maze but not clear because significant decrease in overall activity	[179]
Pentagastrin	Rat	AC	Increase acoustic startle, blocked by CCK B antagonist that also blocked effect of pentagastrin (icv)	[180]

post-training intra-caudate amphetamine injections in the visible platform task. However, pre-retention intra-amygdala lidocaine injections did not block the memory-enhancing effect of post-training intra-amygdala amphetamine injections on either task. Finally, in the hidden platform tasks, post-training intrahippocampal, but not intracaudate, lidocaine injections blocked the memory-enhancing effects of post-training intra-amygdala amphetamine. In the visible platform task, post-training intra-caudate, but not intra-hippocampal, lidocaine injections blocked the memory-enhancing effects of post-training intra-amygdala amphetamine. The findings indicate a double dissociation between the roles of the hippocampus and caudate-putamen in memory and suggest that the amygdala exerts a modulatory influence on both the hippocampal and caudate-putamen memory systems.

Perhaps similarly, lesions of the CeA block freezing but not escape to a tone previously paired with shock, whereas lesions of the basal nucleus of the basolateral complex have just the opposite effect.[194] However, lesions of the lateral nucleus, which receive sensory information required by both measures, block both freezing and escape. Lesions of the basolateral, but not the central nucleus, also block avoidance of a bar associated with shock.[195] It is possible that basolateral outputs to the dorsal or the ventral striatum mediate the escape behavior given the importance of the striatum in several measures of escape or avoidance learning. However, combined, unilateral lesions of each structure on opposite sides of the brain would be required to evaluate whether this results from serial transmission from the basolateral nucleus to the striatum.

The basolateral amygdala to hippocampus pathway as it relates to conditioned and unconditioned fear

As mentioned above, post-training intra-hippocampal as well as intra-amygdala injections of amphetamine selectively enhance memory in a hidden platform water maze task.[192,193] Post training infusion of norepinephrine into the basolateral nucleus enhanced retention in the hidden platform water maze task whereas post training infusion of propranolol had the opposite effect.[196] These results suggest that the amygdala exerts a modulatory influence on hippocampal-dependent memory systems, presumably via direct projections from the basolateral nucleus of the amygdala, perhaps via modulation of long-term potentiation in the hippocampus. Lesions,[197] NMDA antagonists[198] or local anesthetics[199] infused into the basolateral amygdala decrease long-term potentiation in the dentate gyrus of the hippocampus. Conversely, high frequency stimulation of the amygdala facilitates induction of LTP in the dentate gyrus.[200,201] However, combined, unilateral lesions of each structure on opposite sides of the brain would be required to evaluate whether this results from serial transmission from the basolateral nucleus to the hippocampus.

The basolateral amygdala to frontal cortex pathway as it relates to emotion

The importance of the basolateral amygdala in US representation

Following Pavlovian conditioning, presentation of a conditioned stimulus elicits some neural representation of the unconditioned stimulus (US) with which it was paired. For example, the sound of a refrigerator door opening or an electric can opener may bring the family cat into the kitchen in expectation of dinner. Several studies suggest that the Bla, perhaps via connections with cortical areas such as the perirhinal cortex,[202] is critical for these US representations based on studies using a procedure called 'US devaluation'. In these experiments a neutral stimulus (eg a light) is first paired with food so that a conditioned response can be measured. Some animals then have the food paired with something that makes them sick (US devaluation). Following such treatment these animals show a reduction in the conditioned response to the light compared to animals that did not experience US devaluation. This suggests that after conditioning animals have a representation of the value of a reinforcement that is elicited by the cue paired with that US. When that representation is changed, then the behavior elicited by the cue also is changed in the same direction. Lesions of the basolateral, but not the CeA, block US devaluation.[126] In a related paradigm, rats are trained to be fearful of a weak shock in the presence of a tone. When this is followed by presentation of a stronger shock, without further tone-shock pairing, more freezing occurs to the tone. Temporary inactivation of the basolateral amygdala during this *inflation* procedure blocks this effect when testing subsequently occurs with a normal, unlesioned, amygdala.[203]

Second order conditioning also depends on an emotional representation elicited by a conditioned stimulus. In this procedure, cue 1 is paired with a particular US (eg shock or food) and cue 2 is paired with cue 1. After such training, cue 2 elicits a similar behavior as that elicited by cue 1, depending on the US with which cue 1 was paired. Thus it might elicit approach behavior if cue 1 was formerly paired with food, and avoidance if cue 1 was paired with shock. This indicates that cue 1 elicits a representation of the US that then becomes associated with cue 2. Lesions of the basolateral amygdala, but not the CeA, block second order conditioning,[126,189,204] as do local infusions of NMDA antagonists into the basolateral amygdala.[205]

The importance of the basolateral amygdala projection to the frontal cortex in using US representations to guide behavior

Converging evidence now suggests that the connection between the basolateral amygdala and the prefrontal cortex is critically involved in the way in which a US representation (eg very good, pretty good, very bad, pretty bad) guides approach or avoidance behavior. Patients with late or early onset lesions of the orbital regions of the prefrontal cortex fail to use important

information to guide their actions and decision making.[206–208] For example, on a gambling task they choose high, immediate reward associated with long-term loss rather than low, immediate reward associated with positive long-term gains. They also show severe deficits in social behavior and make poor life decisions.

Studies using single unit recording techniques in rats indicate that cells in both the basolateral amygdala and the orbitofrontal cortex fire differentially to an odor, depending on whether the odor predicts a positive (eg sucrose) or negative (eg quinine) US. These differential responses emerge before the development of consistent approach or avoidance behavior elicited by that odor.[209] Many cells in the basolateral amygdala reverse their firing pattern during reversal training (ie the cue that used to predict sucrose now predicts quinine and vice versa),[210] although this has not always been observed.[211] In contrast, many fewer cells in the orbitofrontal cortex showed selectivity before the behavioral criterion was reached and many fewer reversed their selectivity during reversal training.[210] These investigators suggests that cells in the basolateral amygdala encode the associative significance of cues, whereas cells in the orbitofrontal cortex are active when that information, relayed from the basolateral amygdala, is required to guide choice behavior.

Taken together, these data suggest that the connection between the basolateral amygdala and the frontal cortex may be involved in determining choice behavior based on how an expected US is represented in memory. The necessity for communication between the amygdala and frontal cortex recently has been shown in monkeys using a 'disconnection approach' in which the amygdala on one side of the brain and the frontal cortex on the other side are lesioned together.[212] Because the reciprocal connections between the two structures are ipsilateral, this procedure completely eliminates activity of the network connections while preserving partial function of each structure. Using this approach in rhesus monkeys Baxter *et al*[212] found a decrease in US devaluation after unilateral neurotoxic lesions of the basolateal nucleus in combination with unilateral aspiration of orbital prefrontal cortex. These monkeys continued to approach a food on which they had recently been satiated whereas control monkeys consistently switched to the other food.

Neuroimaging studies of the amygdala in humans

The emergence of neuroimaging technologies such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allows the study of the intact, normal amygdala in humans. Analysis of human subjects offers an opportunity to study a component of fear not attainable in animals because in humans it is possible to ask 'Are you afraid?' while presenting stimuli aimed at activating the amygdala. Table 3 presents a list of recent neuroimaging studies demonstrating activation of the human amygdala. It is important to emphasize that the effective spatial resolution of the neuroimaging studies discussed here does not allow for the differentiation of the separate amygdala subnuclei, though the amygdala's role in the modulation of vigilance is most often associated with the CeA (see discussion below).

We will take this opportunity to speculate on what we see as some interesting effects presented in Table 3. Consistent with the animal and human lesion data, presented above, 5 years of human neuroimaging studies support a greater role for the amygdala in the processing of negatively valenced stimuli. Importantly, like much of the animal literature, these early neuroimaging studies are probably limited by the fact that it is difficult to match negatively and positively valenced stimuli for the level of arousal they will evoke. When positively valenced facial expressions have been presented, signal decreases in the amygdala have been reported.[214,217] These data gain support from neuroimaging studies of acupuncture[251] and meditation[252] that also observe signal decreases in the amygdala to these manipulations that could also be categorized as positively valenced. At least two studies have reported that presentation of positively valenced stimuli may be associated with signal increases in the amygdala.[213,231] We note that the Talairach coordinates reported in these two studies were at the dorsal border of the amygdala where it meets the substantia innominata. Signal decreases to positively valenced stimuli observed in other studies were located more ventrally in the traditionally defined amygdala.[214,217] Indeed, a single study has observed both ventral signal decreases and more dorsal signal increases to positively valenced stimuli in the same group of subjects.[217] Clearly, complex responses are occurring to both positively and negatively valenced stimuli throughout the amygdala and the functionally contiguous substantia innominata that will be a challenge to capture with the spatial resolution of current neuroimaging technology.

Given the above discussion concerning signal decreases in the amygdala to positively valenced stimuli it is surprising that studies of amygdala response to the presentation of painful stimuli listed in Table 3 report signal decreases in the amygdala.[253,254] To explain this most interesting finding, we would suggest that perhaps when human subjects have been fully informed about the painful stimulus they are about to receive, eventual presentation of what might be considered a relatively mildly painful stimulus is less negative than what they had anticipated. This interpretation is consistent with the notion that the amygdala is especially sensitive to the uncertainty of stimulus contingencies[2,22,264] (see discussion below). Indeed, anticipation of shock often leads to more fear, measured with the fear potentiated startle test in humans, compared to the actual receipt of shock.[265]

Overall, one can see that amygdala activation appears to be reliably produced by presentation of biologically-relevant sensory stimuli, many of which probably induce strong negative emotional states. For example, fMRI signal intensity is greater when subjects view graphic photographs of negative material (eg, mutilated human bodies) compared to when they view

Table 3 Neuroimaging studies assessing amygdala response in normal human subjects (I–III) and patient groups (IV)

I. Learned and/or innate (unmanipulated) stimuli	**Reference**
A. FACES	
1. Increases	
a. Fear faces	
(1) Fear *vs* neutral	213–216
(2) Fear *vs* happy faces	214,217
(3) Fear faces *vs* fixation	217,218
b. Other facial expressions	
(1) Happy *vs* neutral faces	213
(2) Sad *vs* anger faces	219
(3) Fear and anger *vs* neutral faces	220
(4) Anger and happy *vs* neutral faces (amyg/hippo junction)	221
c. Other facial characteristics	
(1) Unfamiliar *vs* familiar neutral faces	222
(2) Eye contact *vs* variable eye contact in neutral faces	223
2. Decreases	
a. Happy faces	
(1) Happy *vs* neutral faces	214
(2) Happy faces *vs* fixation	217
3. Null findings	
a. Fear faces	
(1) No activation to fear *vs* neutral faces	224
b. Anger faces	
(1) No activation to anger *vs* neutral faces	219,224
(2) No activation to anger *vs* sad faces	219
c. Other facial expressions	
(1) No activation to happy *vs* neutral faces	216
(2) No activation to disgust *vs* neutral faces	215,224
(3) No activation to sad *vs* neutral	216,219
B. COMPLEX VISUAL STIMULI	
1. Aversive *vs* neutral pictures	225,226,266
2. Aversive *vs* neutral films	227
3. Aversive *vs* pleasant pictures	228
4. Neutral films (habituated over time)	229
C. MEMORY	
1. Correlation with recall of aversive films	230
2. Correlation with recall of aversive pictures	231
3. Correlation with recall of positive pictures	231
4. Correlation with retrieval of positive and negative *vs* neutral items	232
D. ODOR	
1. Aversive *vs* neutral odors	233
E. TASTE	
1. Aversive *vs* neutral tastes	234
F. WORDS	
1. Increase	
a. Threatening *vs* neutral words (nonrepeating)	235
2. Null Finding	
a. No activation to negative *vs* neutral words (repeating)	236

I. Learned and/or innate (unmanipulated) stimuli	**Reference**
G. PROSODY	
1. Increase	
a. Fearful *vs* neutral voices (amyg/hippo junction)	216
2. Decrease	
a. Fearful *vs* sad, happy and neutral voices	237
H. COGNITIVE PARADIGMS	
1. Unsolvable anagrams *vs* rest	238
I. BIOLOGICAL MOTION	
1. Biological motion pattern *vs* random	239
II. Aversively conditioned (manipulated) stimuli	
A. Correlation with CS+ (snake film) predicting shock *vs* CS–	240
B. CS+ (shape) predicting shock *vs* CS–	241
C. CS+ (neutral face) partially predicting aversive noise *vs* CS–	242
D. CS+ (masked angry face) predicting aversive noise *vs* CS–	243
E. CS (tone) partially predicting aversive noise *vs* CS–	244
F. Instructed CS+ (color) predicting shock *vs* CS–	245
III. State inductions/pharmacological manipulations	
A. INCREASES	
1. Sad state (w/sad face) *vs* neutral state	246–248
2. Happy state (w/happy face) *vs* neutral state	247
3. Procaine injection *vs* saline	249,250
B. DECREASES	
1. acupuncture *vs* rest	251
2. meditation *vs* rest	252
3. pain *vs* warm	253,254
IV. Psychiatric patients	
A. PTSD	
1. Script-driven imagery of combat scenes	255
2. Imagery of combat scenes	256
2. Combat sounds *vs* white noise	257
3. Fear *vs* happy faces (masked)	258
4. Cognitive paradigm (comorbid drug abuse)	259
B. DEPRESSION	
1. Resting blood flow	260
2. Correlation with negative affect	261
C. SOCIAL PHOBIA	
1. Neutral faces *vs* fixation	262
2. CS+ (face) predicting negative odor *vs* CS–	263

neutral pictures.[266] PET metabolic activity within the amygdala increases to negative material presented via film clips[227] and the amount of amygdala activity during film clips predicts later recall.[230] More recently, human amygdala fMRI signal intensities have been shown to be increased during Pavlovian fear conditioning in response to stimuli that predict an aversive event.[241–244]

Compared to the above mentioned stimuli, the presentation of pictures of facial expressions may represent a strategy for observing amygdala response in the absence of strong emotional response. Human subjects presented with pictures of fearful faces do not report being 'afraid' and yet amygdala activity is modulated as a result, suggesting that reported emotion and amygdala activation should not be equated. Indeed, brain regions other than the amygdala (eg insula cortex) demonstrate responses that are more closely correlated with the intensity of fearful facial expressions.[267] In addition, a recent neuroimaging study demonstrated that while presentation of negative sensory stimuli activated the amygdala to a greater degree than an internal negative state induction, it was the internal state induction that produced greater subjective reports of emotion compared to the sensory stimulus presentations.[227] These data are consistent with the fact that initial human neuroimaging studies which have sought to induce negative emotional states do not provide strong support for the notion that the amygdala is a neural substrate for such feelings. The studies that have been most successful in observing amygdala activation during the induction of emotional state, have also utilized presentations of external stimuli (eg facial expressions).[227,246–248] Also see Ref 268, emphazising the role of the amygdala in the encoding of stimulus contingencies *vs* the generation of strong emotional states.[264]

Numerous studies presented in Table 3 suggest that sensory stimuli demonstrating *some* predictive validity in terms of biological import (eg possible threat) appear sufficient to engage the amygdala, even though these stimuli may not be highly arousing. More than affect itself, amygdala activation in response to subtle emotional stimuli such as photographs of facial expressions might represent affective information processing.

In an attempt to further explore this line of reasoning, facial expressions were presented in a manner intended to isolate amygdala involvement during the earliest stages of facial expression processing.[217] A backward masking technique perfected by Öhman and colleagues was used.[269] Very brief presentations of fearful and happy facial expressions (33 ms) were 'masked'—that is, immediately followed by presentations (167 ms) of neutral faces. Most subjects reported seeing neutral 'expressionless' faces, but not any afraid or smiling faces. Despite this lack of recognition, the amygdala demonstrated greater fMRI signal intensity to masked fearful faces compared to masked happy faces. Thus, the response of the amygdala to these social signals was preferential and automatic. In addition, subjects reported that these masked stimuli did not induce any noticeable changes in their state of emotional arousal. Because subjects were unaware that such stimuli would be presented, this study offers preliminary support for the notion that the amygdala constantly monitors the environment for such signals. More than functioning primarily for the production of strong emotional states, the amygdala would be poised to modulate the moment-to-moment vigilance level of an organism.

The role of the amygdala in modulating vigilance

As mentioned earlier, Kapp, Gallager, Holland and colleagues[2,22] have emphasized the importance of the amygdala in attention and vigilance, of which fear may simply be a special, although especially potent example. To elaborate, the same neurons in the CeA that show changes in firing rates to a tone that predicts a shock, also show changes in firing rates that correlate with *spontaneous* fluctuations in cortical neuronal excitability as measured by cortical EEG in animals.[270,271] This is even seen in experimentally-naive animals.

As reviewed exensively by Whalen[264] these data suggest that the amygdala may be especially involved in increasing vigilance by lowering neuronal thresholds in sensory systems. This may occur via activation of cholinergic neurons in the basal forebrain that lower response thresholds of widespread sensory cortical areas through release of acetylcholine.[272–278] In addition, activation of cholinergic, dopaminergic, serotonergic and noradrenergic neurons in the brainstem may have widespread influences on thalamic and subthalamic sensory as well as motor transmission (see Figure 2). If one assumes that an ambiguous stimulus requires the brain to gather more information to decide to approach or avoid that stimulus, one can imagine that a system designed to promote vigilance and attention would show greater activation, the more ambiguous the stimulus. As suggested by Whalen[264] the fact that fearful faces are especially effective in activating the amygdala may reflect the inherent ambiguity of a fearful face, compared for example to an angry face, rather than the exact content of the emotion itself. Thus, angry faces provide information about the *presence* of threat, but they also give some information about the *source* of that threat. Fearful faces provide information about the presence of threat, but give less information about the source of that threat. If, as emphasized by Kapp *et al*[12,22] projections from the amygdala to the basal forebrain function to potentiate additional cortical information processing, then a more ambiguous face should produce greater amygdala activation. Indeed, preliminary neuroimaging data support this hypothesis.[279] When fearful and angry faces were presented to subjects within the same imaging session, responses in the amygdala and basal forebrain were larger to fearful faces when compared directly to angry faces.

If amygdala activation increases vigilance outside of

strong emotional states it may serve this same function when observed during strong emotional states.[264] This line of reasoning would suggest that amygdala activation should be greatest early in training or when reinforcement schedules are variable or when stimulus contingencies change. In each case these stimulus situations are more ambiguous and in need of greater vigilance and attention. In fact, in both non-human and human subjects, several amygdala-mediated responses[44,280] reach their peak during early conditioning trials and subside thereafter.[12,281–283] Powell and colleagues[284] have documented that amygdala-mediated conditioned responses (eg bradycardia) are larger and are maintained longer to partial reinforcement schedules compared to continuous reinforcement schedules.[285] Even more telling is the observation that when stimulus contingencies change (eg when a CS is suddenly not followed by shock at the beginning of extinction), single unit activity in the lateral amygdala nucleus in rats[47] or blood flow in human amygdala[241] re-emerge. This conceptualization would also suggest that animal and human subjects with amygdala lesions should exhibit deficits in their ability to regulate vigilance or generalized arousal in response to biologically-relevant stimuli, consistent with recent findings.[86]

Although these studies indicate that the amygdala is especially activated under conditions of uncertainty, it can continue to be activated, although perhaps to a lesser degree, when conditions or surroundings are considerably less novel. For example, even after 12 daily exposures to a novel startle test cage, c-fos mRNA was significantly elevated in the basolateral and central nucleus of the amygdala.[286] Furthermore, even after extensive over-training, when rats clearly have learned the temporal relationship between light onset and shock onset in training,[287] lesions of the amygdala completely block the expression of conditioned fear.[288,289] Thus, although the amygdala may be especially important early in training, it may still continue to play an important role later on, depending on the task. Perhaps the blood flow and blood oxygen-dependent measures utilized in human neuroimaging studies are more sensitive to neuronal activity associated with response to uncertainty compared to cellular and/or neuronal activity changes resulting from overtraining.[290]

An emphasis on the role of the amygdala in modulating moment-to-moment levels of vigilance in response to uncertainty has important implications for the study of human psychopathology. Hypervigilance is a key symptom of the anxiety disorders. Pathological anxiety may not be a disorder of fear, but a disorder of vigilance. Indeed, early neuroimaging studies implicate the amygdala in psychiatric disorders such as anxiety[255–259,262,263] and depression.[260,261] Highlighting the present argument that amygdala activation should not be equated with the amount of anxiety that these subjects feel, individuals with social phobia demonstrated exaggerated amygdala response to neutral facial expressions though they reported that these expressions did not make them more afraid.[262] Experimental paradigms specifically aimed at highlighting the role of the amygdala in the modulation of vigilance and subsequent affective information processing may implicate the amygdala in the etiology of these disorders. Animal studies attempting to differentiate brain areas involved in stimulus-specific fear *vs* anxiety[161,291] are especially needed.

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