Chapter 42: Emotion

Introduction

ELATION, COMPASSION, SADNESS, FEAR, and anger are commonly considered examples of emotions. These states have an enormous impact on our behavior and well-being. But what exactly is an emotion? Distinguishing different emotion states is difficult and requires an account of the environmentally or internally generated challenge an organism faces as well as its physiological responses. For example, before we can conclude that a rat is in a state of fear, we need to know that the rat is evaluating a specific threatening stimulus (a predator in its environment) and is mounting an adaptive response, such as high arousal and freezing.

Emotions are often represented along two dimensions: valence (ie, pleasantness to unpleasantness) and intensity (ie, low to high arousal), called "core affect" in many psychological theories. However, emotions can also be grouped into categories, such as categories of basic emotions (happiness, fear, anger, disgust, sadness) and categories of more complex emotions that help regulate social or moral behaviors (eg, shame, guilt, embarrassment, pride, jealousy). There is considerable debate about whether all the categories that are in common usage (like the ones just mentioned) will correspond to scientifically useful categories in a future neuroscience of emotion.

Within experimental contexts, the term *emotion* is used in several different ways, often related to the ways in which emotion is measured (Box 42–1). In everyday conversation, most people use the term "emotion" synonymously with "conscious experience of emotion" or "feeling," and most psychological studies in humans have focused on this sense of "emotion" as well. Most research in animals has focused instead on specific behavioral or physiological responses, in good part because it is impossible to obtain verbal reports in animal studies. Yet emotions have been conserved throughout the evolution of species, as Charles Darwin first observed in his seminal book, *The Expression of the Emotions in Man and Animals.* The empirical approach we describe in this chapter thus considers emotions as central brain states that can be studied in humans as well as many other animals, provided that we distinguish between emotions and feelings.

Box 42–1 Ways of Measuring Emotion

Measures Commonly Used in Humans

Psychophysiology. Psychophysiology uses several measures to assay the physiological parameters associated with emotional states. These measures include autonomic responses (Chapter 41) as well as some somatic responses. The most commonly used measure is the galvanic skin response (also known as the skin conductance response), a measure of sympathetic autonomic arousal derived from the sweatiness of the palms of the hands. Other measures include heart rate, heart rate variability, blood pressure, respiration, pupil dilation, facial electromyography (EMG), and the startle response (see below). Some of these measures mostly correlate with basic dimensions of emotion, such as valence (eg, the magnitude of the startle response) or arousal (eg, the galvanic skin response), whereas others (eg, facial EMG) can provide more fine-grained information about emotions. Facial expression has been used extensively but has no simple relationship to specific emotions.

Subjective ratings. Subjective ratings are often used in human studies and include categorical and continuous ratings (Table 42–1). These ratings can range along emotion dimensions, such as valence (pleasantness/unpleasantness), or the intensity of specific emotions. Subjective ratings necessarily depend on culture-specific words and concepts for emotions.

Experience sampling. Psychologists use experience sampling to quantify the emotions that people actually experience in everyday life. Participants might have their cell phone sound an alarm every few hours, and they then have to stop whatever activity they are doing and fill out a brief questionnaire about what they are feeling at the moment. In this way, a plot of the data can characterize how people's emotions change throughout the day or over longer periods. It turns out that we are actually fairly good at predicting what emotion people will feel next, from knowing how they currently feel.

Hormonal measures. Hormonal responses to emotional states are typically slower than psychophysiological measures. Emotion researchers measure a variety of hormones to assay emotional states over these lengthy periods. Relatively undifferentiated arousal responses are used to evaluate stress. The stress hormone cortisol (Chapter 61) is easily measured from people's saliva.

Specific experimental probes. Several specific behavioral and physiological assays are used to probe emotions with specific stimuli. These assays generally fall within the field of psychophysiology. A common measure is the amplitude of a subject's eyeblink (or other startle reflexes) when a loud sound is presented. This is potentiated when the subject is in a negatively valenced emotional state. Potentiation of the startle reflex is often used to assay the level of anxiety in people, and the same measure has also been validated in animals.

Measures Commonly Used in Nonhuman Animals

Innate behavioral responses. Animals often exhibit stereotyped behaviors as a consequence of certain emotional states. Observing and scoring the behavior is one method of measuring emotional behaviors. Such behaviors can include approaching a stimulus that is rewarding or that promises reward in the future (a positively valenced emotional state), as well as avoiding or defending against threatening stimuli (a negatively valenced emotional state). In addition, analysis of facial expressions can be utilized in many animal model systems, and has even been used for mice.

Psychophysiology and specific experimental probes. As in the case of humans, animal studies can use several psychophysiological measures (eg, heart rate, respiratory rate, galvanic skin response, pupil diameter, startle). In addition, specific behavioral assays have been developed in animals, often derived from initial observations of their innate behavioral responses. Behaviors such as freezing, attacking, exploring, approaching, and hiding can be measured in response to well-controlled experimental stimuli that are designed to induce certain emotional states. The correspondence between human and animal behaviors, which Charles Darwin originally noted in his 1872 book *The Expression of the Emotions in Man and Animals*, provides powerful animal models for investigating human emotions and their pathology.

Table 42–1

Common Questionnaires Used to Assess Fear in Human Emotion Studies

Questionnaire	Type of fear questions
Fear Survey Schedule II	Probes an individual's level of fear across a range of different objects and situations that commonly evoke fear
Fear of Negative Evaluation Scale	Measures fear of being evaluated negatively by others
Social Avoidance and Distress Scale	Measures fear of social situations
Anxiety Sensitivity Index	Measures fear of experiencing different bodily sensations and feelings
Beck Anxiety Inventory	Measures fear and panic-related symptoms experienced over the prior week
Albany Panic and Phobia Questionnaire	Has the subject estimate the amount of fear they would experience in different situations
Fear Questionnaire	Measures the degree of avoidance due to fear
PANAS-X Fear (general)	Measures how much, in general, a person feels fear-related affective states
PANAS-X Fear (moment)	Measures how much, during the present moment, a person feels fear-related affective states

PANAS, Positive and Negative Affect Schedule.

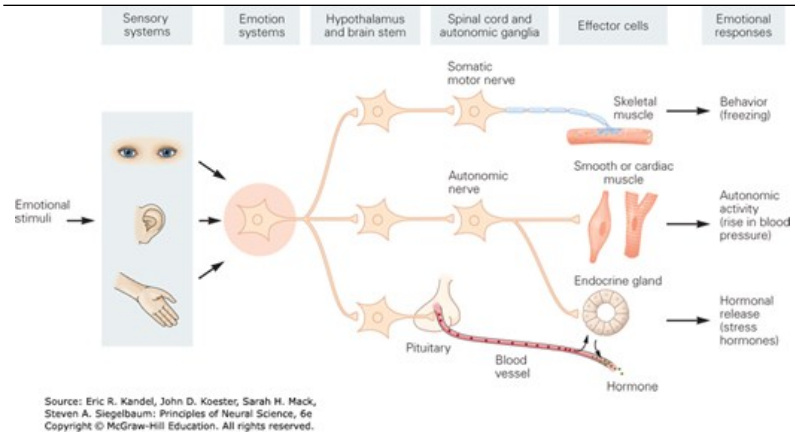
Emotion states typically cause a broad range of physiological responses that occur when the brain detects certain environmental situations. These physiological responses are relatively automatic, yet depend on context, and occur within the brain as well as throughout the body. In the brain, they involve changes in arousal levels and in cognitive functions such as attention, memory processing, and decision making. Somatic responses involve endocrine, autonomic, and musculoskeletal systems (Chapter 41). In sum, emotions are neurobiological states that cause coordinated behavioral and cognitive responses triggered by the brain. This can occur when an individual detects a significant stimulus (positively or negatively charged) or has a specific thought or memory that leads to an endogenously generated emotion state.

Some stimuli—objects, animals, or situations—trigger emotions without the organism having to learn anything about those stimuli. Such stimuli have innately reinforcing qualities and are called unconditioned stimuli; examples are a painful shock or a disgusting taste. However, the vast majority of stimuli acquire their emotional significance through associative learning.

When an individual detects an emotionally significant stimulus, three physiological systems are engaged: the endocrine glands, the autonomic motor system, and the musculoskeletal system (Figure 42–1). The endocrine system is responsible for the secretion and regulation of hormones into the bloodstream that affect bodily tissues and the brain. The autonomic system mediates changes in the various physiological control systems of the body: the cardiovascular system, the visceral organs, and the tissues in the body cavity (Chapter 41). The skeletal motor system mediates overt behaviors such as freezing, fight-or-flight, and particular facial expressions. Together, these three systems control the physiological expression of emotion states in the body.

Figure 42–1

Neural control of emotional responses to external stimuli. External stimuli processed by sensory systems converge on "emotion systems" (eg, the amygdala). If the stimuli are emotionally salient, the emotion systems are activated, and their outputs are relayed to hypothalamic and brain stem regions that control physiological responses, including skeletomuscular action, autonomic nervous system activity, and hormonal release. The figure shows some responses associated with fear. It omits many of the complexities of emotion (eg, the effects of emotion states on cognition).



We begin this chapter with a discussion of the historical antecedents of modern research on the neuroscience of emotion. We then describe the neural circuits and cellular mechanisms that underlie the most thoroughly studied emotion, fear, and in so doing, we will focus on the amygdala. However, it is important to note that there does not appear to be any single brain structure that participates in only one emotion. For instance, the amygdala, which has been known to participate in negatively valenced emotions, also plays a central role in positively valenced emotions: Distinct populations of neurons within the amygdala process positively valenced versus negatively valenced stimuli. We briefly review how emotion states can be changed through extinction and regulation and how emotion interacts with other cognitive processes. We conclude with a survey on the relevance of emotion research to understanding psychiatric disorders.

The Modern Search for the Neural Circuitry of Emotion Began in the Late 19th Century

The modern attempt to understand emotions began in 1890 when William James, the founder of American psychology, asked: What is the nature of fear? Do we run from the bear because we are afraid, or are we afraid because we run? James proposed that the conscious feeling of fear is a consequence of the bodily changes that occur during the act of running away—we feel afraid because we run. James's *peripheral feedback theory* drew on the knowledge of the brain at the time, namely, that the cortex had areas devoted to movement and sensation (Figure 42–2). Little was known at that time about specific areas of the brain responsible for emotion and feeling, but James's view is still debated to this day.

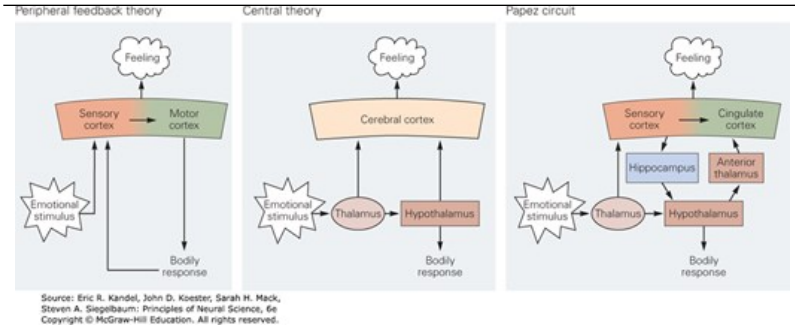
Figure 42–2

Early theories of the emotional brain. (Adapted, with permission, from LeDoux 1996.)

William James's peripheral feedback theory. James proposed that information about emotionally competent stimuli is processed in sensory systems and transmitted to the motor cortex to produce responses in the body. Feedback signals to the cortex convey sensory information about the body responses. The cortical processing of this sensory feedback is the "feeling," according to James.

The Cannon-Bard central theory. Walter Cannon and Philip Bard proposed that emotions are explained by processes within the central nervous system. In their model, sensory information is transmitted to the thalamus where it is then relayed to both the hypothalamus and the cerebral cortex. The hypothalamus evaluates the emotional qualities of the stimulus, and its descending connections to the brain stem and spinal cord give rise to somatic responses, while the thalamocortical pathways give rise to conscious feelings.

The Papez circuit. James Papez refined the Cannon-Bard theory by adding additional anatomical specificity. He proposed that the cingulate cortex is the cortical region that receives hypothalamic output in the creation of feelings. The outputs of the hypothalamus reach the cingulate via the anterior thalamus, and the outputs of the cingulate reach the hypothalamus via the hippocampus.

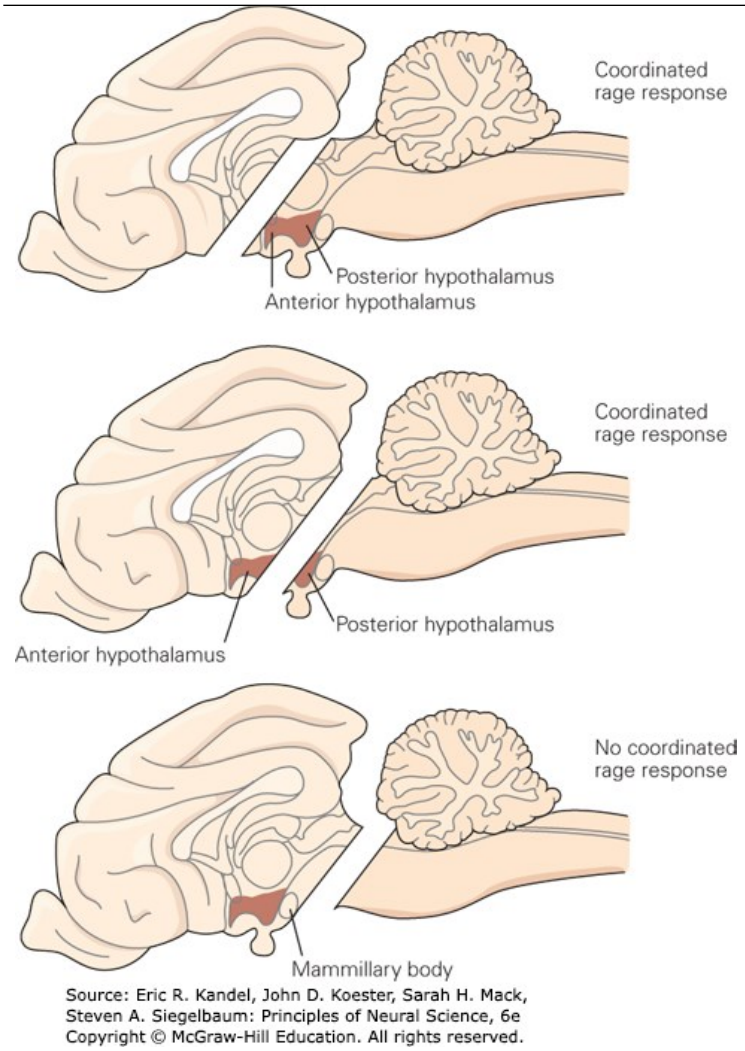


At the turn of the 20th century, researchers found that animals were still capable of emotional responses after the complete removal of the cerebral hemispheres, demonstrating that some aspects of emotion are mediated by subcortical regions. The fact that electrical stimulation of the hypothalamus could elicit autonomic responses similar to those that occur during emotional responses in an intact animal suggested to Walter B. Cannon that the hypothalamus might be a key region in the control of fight-or-flight responses and other emotions.

In the 1920s, Cannon showed that transection of the brain above the level of the hypothalamus (by means of a cut that separates the cortex, thalamus, and anterior hypothalamus from the posterior hypothalamus and lower brain areas) left an animal still capable of showing rage. By contrast, a transection below the hypothalamus, which left only the brain stem and the spinal cord, eliminated the coordinated reactions of natural rage. This clearly implicated the hypothalamus in organizing emotional reactions. Cannon called the hypothalamically mediated reactions “sham rage” because these animals lacked input from cortical areas, which he assumed were critical for the emotional experience of “real” rage (Figure 42–3).

Figure 42–3

Sham rage. An animal exhibits sham rage following transection of the forebrain and the disconnection of everything above the transection (**top**) or transection at the level of the anterior hypothalamus and the disconnection of everything above it (**middle**). Only isolated elements of rage can be elicited if the posterior hypothalamus also is disconnected (**bottom**). This work derives from historical lesion studies in animals. More recent work suggests a more complex picture, in which the hypothalamus is intimately involved in creating the emotion state itself, not merely its behavioral expression.



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

Cannon and his student Phillip Bard proposed an influential theory of emotion centered on the hypothalamus and thalamus. According to their theory, sensory information processed in the thalamus is sent both to the hypothalamus and to the cerebral cortex. The projections to the hypothalamus were thought to produce emotional responses (through connections to the brain stem and spinal cord), while the projections to the cerebral cortex were thought to produce conscious feelings (Figure 42–2). This theory implied that the hypothalamus is responsible for the brain's evaluation of the emotional significance of external stimuli and that emotional reactions depend on this appraisal.

In 1937, James Papez extended the Cannon-Bard theory. Like Cannon and Bard, Papez proposed that sensory information from the thalamus is sent to both the hypothalamus and the cerebral cortex. The descending connections to the brain stem and spinal cord give rise to emotional responses, and the ascending connections to the cerebral cortex give rise to feelings. But Papez went on to expand the neural circuitry of feelings considerably beyond the Cannon-Bard theory by interposing a new set of structures between the hypothalamus and the cerebral cortex. He argued that signals from the hypothalamus go first to the anterior thalamus and then to the cingulate cortex, where signals from the hypothalamus and sensory cortex converge. This convergence accounts for the conscious experience of feeling in Papez's theory. The sensory cortex then projects to both the cingulate cortex and the hippocampus, which in turn makes connections with the mammillary bodies of the hypothalamus, thus completing the loop (Figure 42–2).

The hypothalamus is currently receiving intense interest in studies of emotion in animals, particularly in experiments using optogenetics to manipulate the activity of precise cell populations. These studies have shown that specific populations in the mouse ventromedial hypothalamus are necessary and sufficient for defensive emotion states. Thus the hypothalamus does not merely orchestrate emotional behaviors, but is part of the neural circuitry that constitutes the emotion state itself. The role of the hypothalamus in emotion is much less studied in humans, in part because functional magnetic resonance imaging (fMRI) does not have the spatial resolution to investigate specific hypothalamic nuclei, let alone neuronal subpopulations within them.

In the late 1930s, Heinrich Klüver and Paul Bucy removed the temporal lobes of monkeys bilaterally, thus lesioning all temporal cortex as well as subcortical structures like the amygdala and hippocampus, and found a variety of psychological disturbances, including alterations in feeding habits (the monkeys put inedible objects in their mouth) and sexual behavior (they attempted to have sex with inappropriate partners, like members of other species). In addition, the monkeys had a striking lack of concern for previously feared objects (eg, humans and snakes). This remarkable set of findings came to be known as the Klüver-Bucy syndrome and already suggested that the amygdala might be important for emotion (although it was not the only structure lesioned in these experiments).

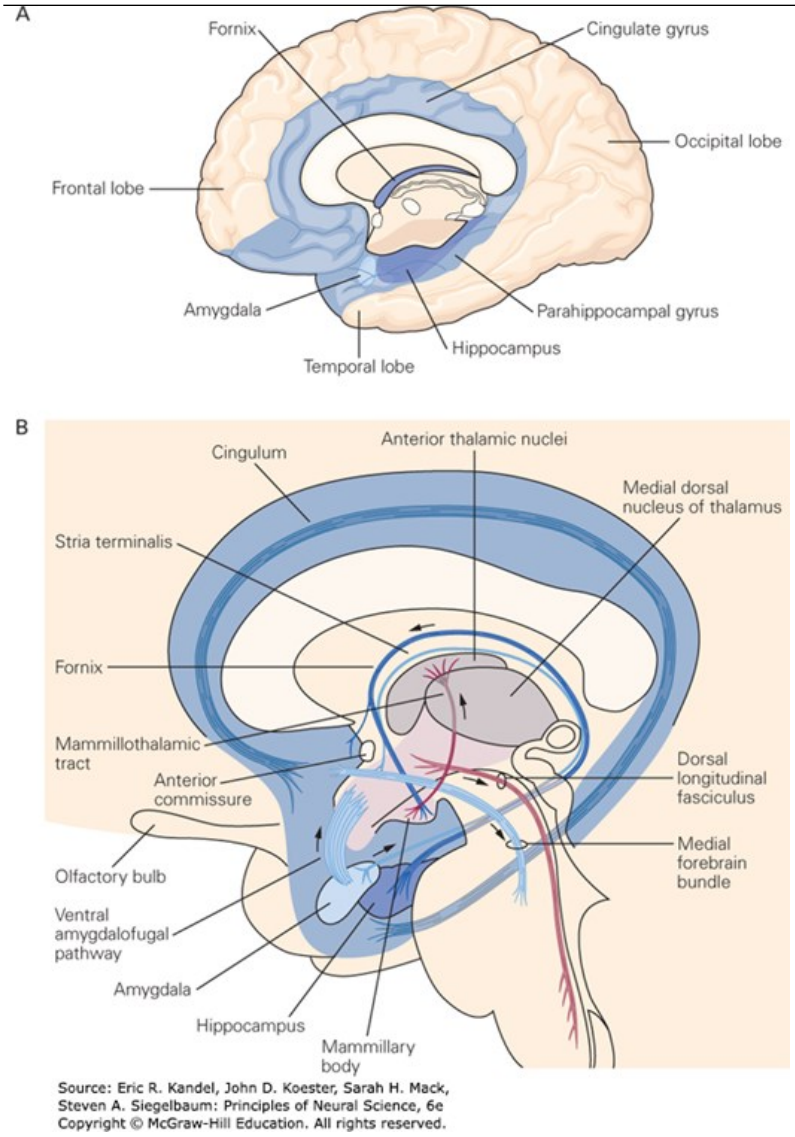
Building on the Cannon-Bard and Papez models and the findings of Klüver and Bucy, Paul MacLean suggested in 1950 that emotion is the product of the "visceral brain." According to MacLean, the visceral brain includes the various cortical areas that had long been referred to as the limbic lobe, so named by Paul Broca because these areas form a rim (Latin *limbus*) in the medial wall of the hemispheres. The visceral brain was later renamed the *limbic system*. The limbic system includes the various cortical areas that make up Broca's limbic lobe (especially medial areas of the temporal and frontal lobes) and the subcortical regions connected with these cortical areas, such as the amygdala and hypothalamus (Figure 42–4).

Figure 42–4

The limbic system consists of the limbic lobe and deep-lying structures. (Adapted, with permission, from Nieuwenhuys et al. 1988.)

A. This medial view of the brain shows the prefrontal limbic cortex and the limbic lobe. The limbic lobe consists of primitive cortical tissue (**blue**) that encircles the upper brain stem as well as underlying cortical structures (hippocampus and amygdala).

B. Interconnections of the deep-lying structures included in the limbic system. The **arrows** indicate the predominant direction of neural activity in each tract, although these tracts are typically bidirectional.



MacLean intended his theory to be an elaboration of Papez's ideas. Indeed, many areas of MacLean's limbic system are parts of the Papez circuit. However, MacLean did not share Papez's view that the cingulate cortex was the seat of feelings. Instead, he thought of the hippocampus as the part of the brain where the external world (represented in sensory regions of the lateral cortex) converged with the internal world (represented in the medial cortex and hypothalamus), allowing internal signals to give emotional weight to external stimuli and thereby to conscious feelings. For MacLean, the hippocampus was involved both in the expression of emotional responses in the body and in the conscious experience of feelings.

Subsequent findings raised problems for MacLean's limbic system theory. In 1957, it was found that damage to the hippocampus, the keystone of the limbic system, produced deficits in converting short- to long-term memory, a function that is distinct from emotions. In addition, animals with damage to the hippocampus are able to express emotions, and humans with hippocampal lesions appear to express and feel emotions normally. In general, damage to areas of the limbic system did not have the expected effects on emotional behavior.

Several of MacLean's other ideas on emotion are nevertheless still relevant. MacLean thought that emotional responses are essential for survival and therefore involve relatively primitive circuits that have been conserved in evolution, an idea already proposed by Charles Darwin almost a century earlier. This notion is key to an evolutionary perspective of emotion. It is now clear that emotions are processed by many subcortical and cortical regions and that the limbic system is by no means the primary system for emotion. Nonetheless, one component of the original limbic system, the amygdala, has received the most attention in studies of both humans and animals. Today, the role of the amygdala in learned fear is probably the best worked-out example of emotion processing in a specific brain structure, and therefore, we consider it next.

The Amygdala Has Been Implicated in Both Learned and Innate Fear

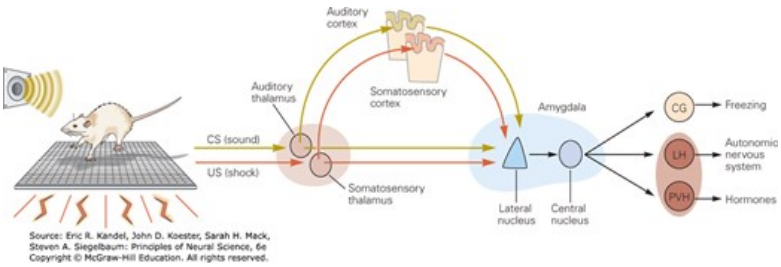
In Pavlovian fear conditioning, an association is learned between an unconditioned stimulus (US) (eg, electric shock) and a conditioned stimulus (CS) (eg, a tone) that predicts the US. For example, if an animal is presented with an emotionally neutral CS (a tone) for several seconds and then shocked during the final second of the CS, especially if this pairing of tone and shock is repeated several times, presentation of the tone alone will elicit defensive freezing and associated changes in autonomic and endocrine activity. In addition, many defensive reflexes, such as eyeblink and startle, will be facilitated by the tone alone.

Research in many laboratories has established that the amygdala is necessary for Pavlovian fear conditioning: Animals with amygdala damage fail to learn the association between the CS and the US and thus do not express fear when the CS is later presented alone.

The amygdala consists of approximately 12 nuclei, but the lateral and central nuclei are especially important in fear conditioning (Figure 42–5). Damage to either nucleus, but not to other regions, prevents fear conditioning. The lateral nucleus of the amygdala receives most sensory input (but the medial nucleus receives olfactory input), including sensory information about the CS (eg, a tone) from both the thalamus and the cortex. The cellular and molecular mechanisms within the amygdala that underlie learned fear, especially in the lateral nucleus, have been elucidated in great detail. The findings support the view that the lateral nucleus is a site of memory storage in fear conditioning. Neurons in the central nucleus, by contrast, mediate outputs to brain stem areas involved in the control of defensive behaviors and associated autonomic and humoral responses (Chapter 41). The lateral and central nuclei are connected by way of several local circuits within the amygdala, including connections with the basal and intercalated masses. The actual circuitry for Pavlovian learning is thus considerably more complex than what is indicated by Figure 42–5, involving multiple relays among amygdala regions.

Figure 42–5

Neural circuits engaged during fear conditioning. The conditioned stimulus (**CS**) and unconditioned stimulus (**US**) are relayed to the lateral nucleus of the amygdala from the auditory and somatosensory regions of the thalamus and cerebral cortex. Convergence of the CS and US pathways in the lateral nucleus is believed to underlie the synaptic changes that mediate learning. The lateral nucleus communicates with the central nucleus both directly and through intra-amygdala pathways (not shown) involving the basal and intercalated nuclei. The central nucleus relays these signals to regions that control various motor responses, including the central gray region (**CG**), which controls freezing behavior; the lateral hypothalamus (**LH**), which controls autonomic responses; and the paraventricular hypothalamus (**PVH**), which controls stress hormone secretion by the pituitary–adrenal axis. (Adapted from Medina et al. 2002.)



Sensory inputs reach the lateral nucleus from the thalamus both directly and indirectly. Much as predicted by the Cannon-Bard hypothesis, sensory signals from thalamic relay nuclei are conveyed to sensory areas of cerebral cortex. As a result, the amygdala and cortex are activated simultaneously. However, the amygdala is able to respond to an auditory danger cue before the cortex can fully process the stimulus information. This scheme is well worked out only for auditory fear conditioning in rodents, and it remains unclear how it applies to other cases, such as visually evoked fear in humans.

The lateral nucleus is thought to be a site of synaptic change during fear conditioning. The CS and US signals converge on neurons in the lateral nucleus; when the CS and US are paired, the effectiveness of the CS in eliciting action potentials is enhanced. This basic mechanism for a form of associative learning is similar to cellular mechanisms that underlie declarative memory in the hippocampus as well (Chapter 54). In particular, the synaptic plasticity found in the hippocampus has also been demonstrated in specific central amygdala circuits. The central amygdala thus does not simply drive motor outputs but is also part of the circuitry through which fear associations are formed and stored, very likely by transmitting information about the CS and US from the lateral nucleus. Neural plasticity likely also occurs in the basal and accessory basal nuclei during fear learning. As with the hypothalamus, recent work in rodents using tools such as optogenetics to manipulate specific subpopulations of amygdala

neurons has begun to dissect this circuitry in further detail.

The emotional charge of a stimulus is evaluated by the amygdala together with other brain structures, such as the prefrontal cortex. If this system detects danger, it orchestrates the expression of behavioral and physiological responses by way of connections from the central amygdala and parts of prefrontal cortex to the hypothalamus and brain stem. For example, freezing behavior is mediated by connections from the central nucleus to the ventral periaqueductal gray region. In addition, the basal and accessory basal nuclei of the amygdala send projections to many parts of the cerebral cortex, including the prefrontal, rhinal, and sensory cortices; these pathways provide a means for neural representations in the amygdala to influence cognitive functions. For example, through its widespread projections to cortical areas, the amygdala can modulate attention, perception, memory, and decision making. Its connections with the modulatory dopaminergic, noradrenergic, serotonergic, and cholinergic nuclei that project to cortical areas also influence cognitive processing (Chapter 40). Given these very widespread connections and functional effects, the amygdala is well situated to implement one of the key features of an emotion: its coordinated and multicomponent responses.

The Amygdala Has Been Implicated in Innate Fear in Animals

Although the majority of stimuli acquire their emotional significance through learning, especially in humans, many animals also rely on innate (unconditioned) signals in the detection of threats, mates, food, and so forth. For example, rodents exhibit freezing and other defensive behaviors when fox urine is detected. Recent studies have made considerable progress in uncovering the circuits underlying this innate fear.

In mammals, sensory signals of unconditioned threats involving predator or conspecific odors are transmitted from the vomeronasal component of the olfactory system (Chapter 29) to the medial amygdala. This stands in contrast to auditory and visual threats, which as noted above are processed via the lateral amygdala. Outputs of the medial amygdala reach the ventromedial hypothalamus, which connects with the premammillary hypothalamic nucleus. In contrast to learned fear, which depends on the ventral periaqueductal gray region, unconditioned fear responses depend on inputs from the hypothalamus to the dorsal periaqueductal gray region. There are other subcortical systems specialized for processing specific innate threats; for instance, the mouse superior colliculus is involved in detecting aerial predators, such as a hawk flying overhead.

It is difficult to study unconditioned emotional responses in humans because the possibility of learning begins right at birth and cannot be experimentally controlled, and because there appear to be large individual differences. For instance, it is thought that threat-related stimuli such as snakes and spiders may be innately fear-inducing stimuli for those people with phobias toward these animals but not for people who keep them as pets. These large individual differences, and the relative roles of innate and learned fear, are important topics for understanding psychiatric illnesses such as anxiety disorders.

The Amygdala Is Important for Fear in Humans

The basic findings from animal studies regarding the role of the amygdala in emotion have been confirmed in studies of humans. Patients with damage to the amygdala fail to show fear conditioning when presented with a neutral CS paired with a US (electric shock or loud noise). In normal human subjects, activity in the amygdala increases during CS–US pairing, as measured with fMRI.

Studies of rare human patients with bilateral amygdala lesions have led to the surprising finding of a dissociation in fear reactions to exteroceptive and interoceptive stimuli (Figure 42–6). Not only do such patients fail to show any autonomic fear reactions to exteroceptive stimuli, to either the CS or the US, but they also appear to lack any conscious experience of fear, as evidenced either from behavioral observation or through subjective verbal report on a questionnaire. In one study, such a patient was confronted with snakes and spiders in an exotic pet store, with monsters in a haunted house, and with autobiographical recollections of highly traumatic personal events (eg, being threatened with death by another person). In none of these instances was there any evidence of fear, and the patient reported feeling no fear at all (even though the patient was able to feel other emotions). These findings argue that the amygdala is necessary for the induction and experience of fear in humans.

Figure 42–6

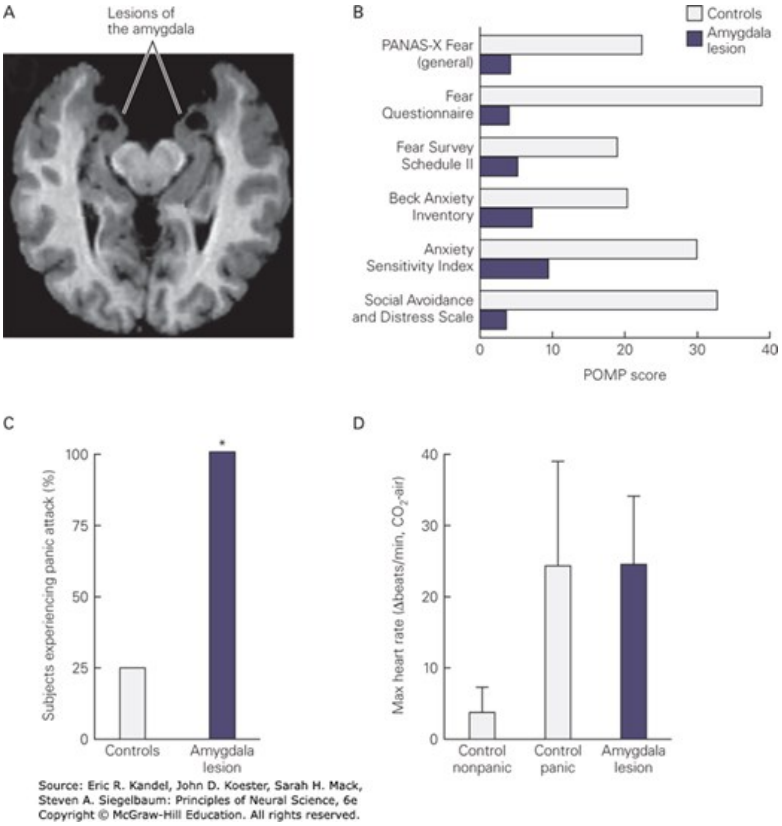
In humans, the amygdala is necessary for fear responses to external, but not internal, stimuli.

A. Magnetic resonance imaging scan of a subject's brain with bilateral amygdala lesions. Lesions were relatively restricted to the entire amygdala, a very rare lesion in humans.

B. The subject with bilateral amygdala lesions, S.M., did not report feeling fear for any of the questionnaire-based measures normally used to assess fear and anxiety (percentage of maximum score possible [**POMP**]). This was consistent with other findings: She did not exhibit fear when watching horror movies, when confronted with large spiders and snakes, or when visiting a haunted house during Halloween. These findings show that the human amygdala is necessary for inducing fear in response to these external stimuli. (Abbreviation: **PANAS**, Positive and Negative Affect Schedule.)

C. By contrast, a study of S.M. and two other subjects with bilateral amygdala lesions found that they exhibited strong panic when given an internal stimulus. They were asked to inhale carbon dioxide (CO_2), which produces a feeling of suffocation. This caused all three patients with amygdala lesions and 3 out of 12 of the control subjects with intact amygdalae to experience panic attacks.

D. Change from baseline in maximum heart rate during CO_2 inhalation relative to air trials. Both the amygdala lesion patients (n = 2) and the control subjects who panicked (n = 3) had higher increases in heart rate than the control subjects who did not panic (n = 9). (Mean ± standard error of the mean.) (Adapted, with permission from Feinstein et al 2011, 2013.)



By striking contrast, the very same patients with amygdala lesions report intense panic when they are made to feel as though they are suffocating (an interoceptive fear cue, achieved by inhaling carbon dioxide, which lowers blood pH). The dissociation of fear reactions to exteroceptive and interoceptive stimuli supports the idea that there are multiple fear systems in the human brain and that the amygdala cannot be the only structure essential for all forms of fear. Ongoing work is providing more insight, such as mapping out the specific amygdala nuclei that are damaged in these patients and which nuclei are responsible for what types of deficits. This level of resolution is standard in animal studies of the amygdala but has been difficult to achieve in humans, since the amygdala lesions cannot be made experimentally but instead must rely on rare patients that reflect accidents of nature. Equally important, there are theoretical frameworks for how to subdivide the different types of fear. For example, fear can be mapped onto a dimension of threat imminence, which may cover a range from threats that are very far away (perhaps evoking mild anxiety, and engaging monitoring and attention), to threats that are more proximal (evoking fear, and engaging responses such as freezing), to threats that are about to cause death (evoking panic, and engaging defensive behaviors). Eventually, we will need to have a more fine-grained mapping between brain systems and varieties of emotion that incorporates all of these details.

Certain forms of fear learning are relatively unique to humans. For example, simply telling a human subject that the CS may be followed by a shock is enough to allow the CS to elicit fear responses. The CS elicits characteristic autonomic responses even though it was never associated with the delivery

of the shock. Humans can also be conditioned by allowing them to observe someone else being conditioned—the observer learns to fear the CS even though the CS or US was never directly presented to the observing subject. Some other animals also are able to learn fear through such observational learning, although this seems to be more rare than is the case in humans. One form of learning that is ubiquitous in humans appears to be unique to our species: active pedagogy, whereby another person teaches somebody that a stimulus is dangerous. While learning what to avoid and what to approach in the world is a large part of development in the young of all species, active teaching about the significance of stimuli has not been found in any species other than humans so far (learning through passive observation is more common).

The emotional learning and memory capacities of the human amygdala fall into the category of *implicit learning* and memory, which includes forms of memory such as the unconscious recall of perceptual and motor skills (Chapter 53). In situations of danger, however, the hippocampus and other components of the medial temporal lobe system that participate in *explicit learning* and memory (the conscious recall of people, places, and things) will be recruited as well and will encode aspects of the learning episode. As a result, the learned indicators of danger can also be recalled consciously, at least in humans and probably in some other species as well.

Studies of patients with bilateral damage to the amygdala or hippocampus illustrate the separate contributions of these structures to implicit and explicit memory for emotional events, respectively. Patients with damage to the amygdala show no conditioned skin-conductance responses to a CS (suggesting no implicit emotional learning) but have normal declarative memory of the conditioning experience (indicating intact explicit learning). By contrast, patients with hippocampal damage show normal conditioned skin-conductance responses to the CS (suggesting intact implicit emotional learning) but have no conscious memory of the conditioning experience (indicating impaired explicit learning).

Amygdala function is altered in a number of psychiatric disorders in humans, especially disorders of fear and anxiety (Chapter 61). In addition, the amygdala plays an important role in processing cues related to addictive drugs (Chapter 43). In all of these cases, the amygdala is but one component of a distributed neural network that includes other cortical and subcortical regions. For instance, declarative memory for highly emotional events involves interactions between the amygdala and hippocampus; motivational consequences of Pavlovian conditioning involve interactions between the amygdala and the ventral striatum; and learning that a previously dangerous stimulus is now safe involves interactions between the amygdala and the prefrontal cortex. An important future direction will be to go beyond examining each component in isolation in order to better understand how emotions are processed by complex multicomponent networks of brain regions. This level of analysis is common in studies of human emotion using fMRI (see below).

The Amygdala's Role Extends to Positive Emotions

Although most work on the neural basis of emotion during the past half century has focused on aversive responses, especially fear, other studies have shown that the amygdala is also involved in positive emotions, in particular the processing of rewards. In monkeys and rodents, the amygdala participates in associating neutral stimuli with rewards (appetitive Pavlovian conditioning), just as it participates in associating neutral stimuli with punishments, and there appear to be distinct populations of neurons that encode rewards and punishments in the amygdala. This is broadly similar to findings from the rodent hypothalamus, where neurons involved in defense and in mating are also close together and only modern molecular techniques can test their independent roles.

Studies in nonhuman primates and rodents have investigated a suggestion first made by Larry Weiskrantz that the amygdala represents stimulus reward as well as punishment. For example, in a recent study, monkeys were trained to associate abstract visual images with rewarding or aversive USs. The meaning was then reversed (eg, by pairing an aversive outcome with a visual image that had previously been associated with a reward). In this way, it was possible to distinguish the role of the amygdala in representing visual information from its role in representing the reinforcement (a rewarding or aversive stimulus) predicted by a visual image. Changes in the type of reinforcement associated with an image modulated neural activity in the amygdala, and the modulation occurred rapidly enough to account for behavioral learning.

Subsequent studies using modern molecular and genetic techniques have demonstrated that distinct circuitry within the amygdala mediates a neural representation of rewarding USs, as well as rewarding experiences. The activation of a neural representation of an appetitive US in the amygdala is sufficient to induce innate valenced physiological responses as well as appetitive learning. Moreover, reactivation of neurons activated earlier by an enjoyable experience appears to be sufficient to elicit positive emotions. These findings are consistent with a growing number of functional imaging studies in humans that have shown that the amygdala is involved in emotions quite broadly. For example, the human amygdala is activated when subjects observe pictures of stimuli associated with food, sex, and money or when people make decisions based on the reward value of stimuli.

Emotional Responses Can Be Updated Through Extinction and Regulation

Once conditioned fear has been learned, it can be extinguished by later experiencing that the CS is now safe, for instance, by repeatedly presenting the CS without any US pairing. The circuitry underlying fear extinction has been studied in detail as it is highly relevant to psychiatric illnesses such as post-traumatic stress disorder (PTSD). Projections from the prefrontal cortex to the amygdala are required to override the conditioned fear in the amygdala. While conditioned fear responses decline during extinction, they are never completely erased, as demonstrated by the phenomenon of reinstatement, where fear can suddenly reappear.

Cognitive therapies for changing emotion states have also been studied, primarily in humans. For instance, a focused effort to increase or decrease the intensity of an emotion like fear has some effect on the emotion state. Indeed, neuroimaging studies have found that people can, to some degree, change their amygdala activation to fear-inducing stimuli just by how they think about those stimuli. Emotion regulation is a complex phenomenon, since there are multiple strategies for changing the emotion, ranging from just suppressing the motor behaviors to better control over how we evaluate a situation. These multiple sources of emotion regulation, especially in humans, highlight the fact that emotions must often be adjusted in keeping with complex social norms.

Emotion Can Influence Cognitive Processes

As evidenced in the above examples, emotion interacts with many other aspects of cognition, including memory, decision making, and attention. We discussed above an example of nondeclarative emotional memory, Pavlovian fear conditioning, but emotions can also influence declarative memory. Projections from the amygdala to the hippocampus can influence how learning is encoded and consolidated into long-term declarative memory. This accounts for why we remember best those events in our lives that are the most emotional, such as weddings and funerals.

Emotion has complex effects on decision making, as one might expect, since the subjective evaluation of such variables as risk, effort, and value is modulated by emotion. For instance, different choices with the same objective risk can elicit different behavioral decisions depending on whether they are framed as a win or a loss. For example, subjects typically prefer a sure gain of $5 to a 50% chance of winning $10, but prefer a 50% chance of losing $10 to a sure loss of $5. Interestingly, fMRI studies have revealed that such framing modulates amygdala activation. There is greater amygdala activation in the “win” frame when subjects choose a sure amount over a risky gamble, and greater amygdala activation in the “loss” frame when subjects choose the gamble over the sure amount. Thus, value representations in the amygdala are not rigidly associated with stimuli but are modulated by context-dependent evaluation.

Because emotionally relevant stimuli are highly salient to an organism’s self-interest, they typically capture attention. For instance, people tend to orient toward, and look at, emotionally relevant visual stimuli, even when those stimuli are presented under conditions where they cannot be consciously perceived. One intriguing finding is that patients with bilateral amygdala lesions are impaired not only in their experience and expression of fear, as described above, but also in their recognition of fear in other people. One such patient, a woman called S.M., was selectively impaired in recognizing fear from facial expressions. This impairment in turn appears to result from a more basic impairment in allocating visual attention to those regions of the face that normally signal fear. S.M. does not spontaneously fixate on the eye region of the face when she looks at facial expressions and therefore does not process detailed visual information from wide eyes that would normally contribute to the recognition of fear when one is looking at a fearful face (Figure 42–7).

Figure 42–7

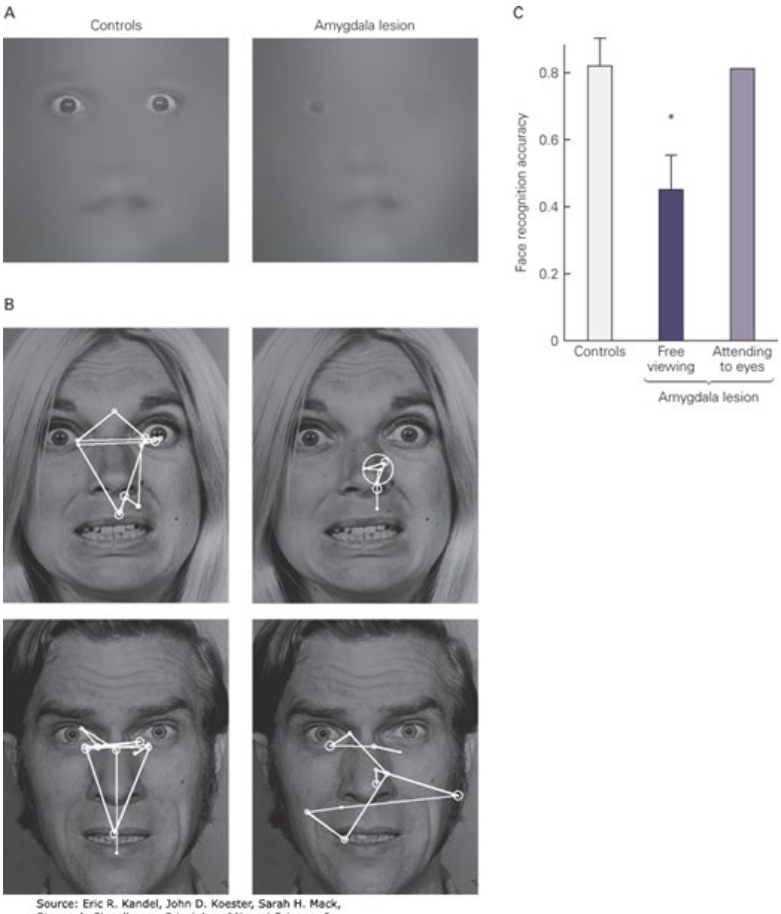
Bilateral amygdala lesions impair the recognition of fear in the facial expressions of others. This impairment may be due to abnormal processing of information from the face. (Reproduced, with permission, from Adolphs et al. 2005.)

A. S.M. made significantly less use of information from the eye region of faces when judging emotion. These images show the regions of the face from which control subjects (*left*) or S.M. (*right*) were able to recognize fear. The results were obtained by showing subjects many trials with only small parts of the face revealed. All those trials in which subjects were able to recognize fear could then be summed to produce an image like this, which shows the regions of the face that viewers make use of in order to discriminate fearful from happy faces (these particular parts of the face allow viewers to tell apart fearful from happy faces, whereas other parts do not help with this discrimination).

B. While looking at whole faces, S.M. (*right*) exhibited abnormal face gaze (indicated by **white lines**), making far fewer fixations to the eyes than did

controls (*left*). This shows that S.M. failed to attend to and hence process visual information from the eye region. This deficit was observed across all emotions, but was most important for fear recognition because wide eyes normally predict fear.

C. S.M. showed poor ability to recognize fear when freely observing whole faces (**free viewing**), but her performance improved remarkably when instructed to look at the eyes (**attending to eyes**). This result shows that the role of the amygdala in processing fearful expressions involves directing attention onto features that are particularly significant (the eyes), rather than the downstream process of interpreting the sensory input.



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

These findings suggest an important role for the amygdala in attention and highlight the possibility that apparently specific deficits for certain emotions (like fear) might arise from more basic attentional or motivational effects. There is ongoing debate about the precise role of the human amygdala in attentional aspects of emotion processing: Some studies argue that it comes into play even for nonconscious threat-related stimuli and in a very automatic fashion; other studies argue that the amygdala requires more elaborated and conscious processing once attention has already been allocated. Single-neuron recordings from the human amygdala support the latter view, whereas some fMRI studies support the former view. All of the findings from human lesion studies will need to be more finely dissected; some recent work on patients who have damage only to specific amygdala subnuclei is yielding further insights.

Many Other Brain Areas Contribute to Emotional Processing

As seen in the case of conditioned and unconditioned fear, the amygdala contributes to emotional processing as part of a larger circuit, or set of circuits, that includes regions of the hypothalamus and brain stem, eg, the periaqueductal gray region in the brain stem. Cortical areas are also important components of this circuit.

A number of human studies have implicated the ventral region of the anterior cingulate cortex, the insular cortex, and the ventromedial prefrontal cortex in various aspects of emotional processing. The medial prefrontal cortex and amygdala are closely connected with one another, and neurons in these brain regions show complex responses that encode information about many emotional and cognitive variables. These findings contribute to an

emerging picture of a dynamic neural substrate for emotion states: Individual states are not the outcome of a single structure or specific neurons, but are more flexibly assembled over a distributed population of multifunction neurons.

Some emotions are associated with social interaction and range from empathy and pride to embarrassment and guilt. Like the primary emotions such as fear, pleasure, or sadness, these social emotions produce various bodily changes and behaviors and can be experienced consciously as distinct feelings. This class of emotions may depend especially on cortical regions in the prefrontal cortex.

Studies of patients with neurological disease and focal brain lesions have advanced the understanding of the neural circuitry of emotions (Box 42–2). For example, damage to some sectors of the prefrontal cortex markedly impairs social emotions and related feelings. In addition, these patients show marked changes in social behavior that resemble the behavior of patients with developmental sociopathic personalities. Patients with damage to some sectors of the prefrontal cortex are unable to hold jobs, cannot maintain stable social relationships, are prone to violate social conventions, and cannot maintain financial independence. It is common for family ties and friendships to break after the onset of this condition. Recent studies reveal that, under controlled experimental conditions, the moral judgments of these patients can also be flawed.

Box 42–2 Lesion Studies of Emotion

Examination of patients with focal lesions complements neuroimaging studies of the neural correlates of emotions. In addition to studies of the amygdala, lesion studies have provided insights into the role of several other brain regions in processing emotions.

One of the most famous set of studies harks back to the accident of Phineas Gage, who in 1848 suffered an injury to his ventromedial prefrontal cortex. Gage was working on constructing a railway in Vermont and was tamping gunpowder into a hole with a long metal rod, called a tamping iron. By accident, he struck a spark in the rock and the gunpowder exploded, shooting the tamping iron straight through his head.

Amazingly, Gage lived for many years after this horrible accident, but he was a changed person with notable changes in his social and emotional behavior. This was the first evidence that parts of the prefrontal cortex played a role in emotions. Since Gage, several patients with damage centered on the ventromedial prefrontal cortex have been described. These patients have poor insight and decision-making abilities and tend to have blunted or unusual emotional responses, especially for social emotions.

Unlike normal individuals, patients with these frontal lesions do not exhibit changes in heart rate or degree of palm sweating when shown pictures that have emotional content, although they can describe the pictures flawlessly. Likewise, patients with frontal lesions do not show skin conductance changes, a sign of sympathetic activation, during the period that precedes making risky and disadvantageous decisions, suggesting that their emotional memory is not engaged during that critical period. Also unlike normal subjects, these patients fail in tasks in which they have to make a decision under conditions of uncertainty, and in which reward and punishment are important factors.

Several brain regions are also more specifically involved in feelings. Damage to the right somatosensory cortex (primary and secondary somatosensory cortices and insula) impairs social feelings such as empathy. Consistent with this finding, patients with lesions in the right somatosensory cortex fail to guess accurately the feelings behind the facial expressions of other individuals. This ability to read faces is not impaired in patients with comparable lesions of the *left* somatosensory cortex, indicating that the right cerebral hemisphere is dominant in the processing of at least some feelings. Body sensations such as pain and itch remain intact, as do feelings of basic emotions such as fear, joy, and sadness.

On the other hand, damage to the human insular cortex, especially on the left, can suspend addictive behaviors, such as smoking. This suggests that the insular cortices play a role in associating external cues with internal states such as pleasure and desire. Interestingly, complete bilateral damage to the human insular cortices, as caused by herpes simplex encephalitis, does not eliminate emotional feelings or body sensations, suggesting that the somatosensory cortices and subcortical nuclei in the hypothalamus and brain stem are also involved in generating feeling states.

Patients with medial and ventral frontal lobe damage, unlike patients with more dorsal or lateral frontal lobe damage, do not have motor defects such as limb paralysis or speech defects and thus may appear at first to be neurologically normal. Their perceptual abilities, attention, learning, recall, language, and motor abilities often show no signs of disturbance. Some patients have IQ scores in the superior range. For these reasons, they sometimes attempt to return to their work and social activities after their initial recovery from brain damage. Only when they start to interact with

others are their defects noticed.

In the prefrontal cortex, the ventromedial sector is particularly important for such interactions. In most patients with impaired social emotions, this sector is damaged bilaterally, although damage restricted to the right side can be sufficient to cause impairments. The critical region encompasses Brodmann's areas 12, 11, 10, 25, and 32, which receive extensive projections from the dorsolateral and dorsomedial sectors of the prefrontal cortex. Some of these areas project extensively to subcortical areas related to emotions: the amygdala, the hypothalamus, and the periaqueductal gray region in the brain stem.

Interestingly, when asked about punishment, reward, or responsibility, adult patients with damage to the ventromedial prefrontal cortex often respond as if they still have the basic knowledge of the rules, but their actions indicate that they fail to use them in real-life situations. This dissociation suggests that their behavioral defects are not caused by a loss of factual knowledge but rather by impairment of the brain's assignment of motivational value to factors that normally exert control over behavior. In some respects, this dissociation is similar to the dissociation between explicit and implicit emotional learning vis-à-vis the hippocampus and the amygdala. An interesting hypothesis arising from these dissociations is that one might find greater deficits following lesions to emotion-related structures, like the amygdala or ventromedial prefrontal cortex, in other species, or in children, in whom explicit behavioral control has not yet evolved or developed to the degree that it has in adults. There is some support for this idea: Lesions to these structures early in life can result in more severe deficits in emotional and social behaviors than if the lesions are sustained in adulthood (a pattern opposite to that of most other lesions, which show better recovery of function the earlier the onset). These findings also suggest hypotheses for neural dysfunction that may contribute to the emotional difficulties seen in developmental psychiatric disorders, such as autism.

The above lesion studies have been complemented by controlled experimental studies using fMRI, which provide further insight into mechanisms. Functional imaging of value-based decision making in healthy human subjects shows that the ventromedial prefrontal cortex is activated during the period before making a choice. That same region is activated also just by the administration of punishment and reward, supporting the notion that the emotional significance of anticipated punishments and rewards is computed as part of the mechanism that guides this kind of decision making. Punishment and reward are frequently featured in experiments involving economic and moral decisions, and such decision making prominently involves many of the same structures that are also involved in processing emotions.

The prefrontal cortex, especially areas in the ventromedial sector, operates in parallel with the amygdala. During an emotional response, ventromedial areas govern the attention accorded to certain stimuli, influence the content retrieved from memory, and help shape mental plans for responding to the triggering stimulus. By influencing attention, both the amygdala and the ventromedial prefrontal cortex are also likely to alter cognitive processes, for example, by speeding up or slowing down the flow of sensory representations (Chapter 17).

Functional Neuroimaging Is Contributing to Our Understanding of Emotion in Humans

Neuroimaging studies of emotions typically use fMRI. These studies have contributed to our understanding of emotion in three important ways. First, they have begun to dissociate and experimentally manipulate specific aspects of emotion, such as feelings, value, or concepts of emotions. These studies are beginning to show how all these different aspects can be coordinated by activity in different brain regions.

Second, fMRI studies on emotion have been accumulating at an ever-increasing pace, and much of the data from such studies are now widely available. This provides the opportunity for meta-analyses of many studies, avoiding the limitations that may be inherent in any one study in isolation. For instance, some meta-analyses have confirmed the role of the ventromedial prefrontal cortex in representing value for many different kinds of stimuli, including food and money. Other meta-analyses have suggested that specific basic emotions (eg, fear, anger, or happiness) activate a widely distributed and overlapping set of brain regions, confirming the view that no brain structure is responsible for a single emotion.

Finally, fMRI studies have begun to use novel methods in their analyses. For example, the pattern of activation seen across many voxels in a brain region, rather than the mean level of activation in that region, is used to train powerful machine-learning algorithms to classify emotion states. This approach is demonstrating that it is possible to decode specific emotion states from distributed patterns of brain activation.

Functional Imaging Has Identified Neural Correlates of Feelings

Conscious experiences of an emotion are generally referred to as feelings. Evidence for the neural correlates of feelings comes primarily from functional imaging studies of humans and from neuropsychological testing of patients with specific brain lesions. A main challenge for these studies is in dissociating the conscious experience of the emotion from other aspects of the emotion, such as the elicitation of physiological responses, since

these tend to occur contemporaneously. Another challenge is how to connect such studies with studies of emotion in animals, where we have no agreed-upon dependent measures to assay what they consciously experience.

One early functional imaging study used positron emission tomography to test the idea that feelings are correlated with activity in those cortical and subcortical somatosensory regions that specifically receive inputs related to the internal environment—the viscera, endocrine glands, and musculoskeletal system. Healthy subjects were asked to recall personal episodes and to attempt to reexperience as closely as possible the emotions that accompanied those events. Activity changed in many regions known to represent and regulate body states, such as the insular cortex, secondary somatosensory cortex (S-II), cingulate cortex, hypothalamus, and upper brain stem. These results support the idea that at least a part of the neural substrate for feelings involves brain regions that regulate and represent bodily states, a finding that bears some resemblance to the hypothesis of William James mentioned earlier, that feelings are based on an awareness of bodily reactions.

The importance of both cortical and subcortical structures in processing feelings is also borne out by more recent fMRI studies. One such study examined the feeling of fear induced by anticipation of electrical shock (Figure 42–8). In this study, subjects lay in the scanner while they saw a game on a video screen in which a virtual predator (a red dot) gets closer to the subject. Once the predator caught them, they could receive a painful electric shock to the hand. The anxiety produced when the predator was some distance away was associated with activation of the medial prefrontal cortex; as the predator closed in, the periaqueductal gray became activated, and this was correlated with reports by the subjects of a feeling of dread. This finding supports a role for the medial prefrontal cortex in planning and anticipation related to a distant threat and a role for the periaqueductal gray in mounting the defensive responses required for coping with an immediate threat.

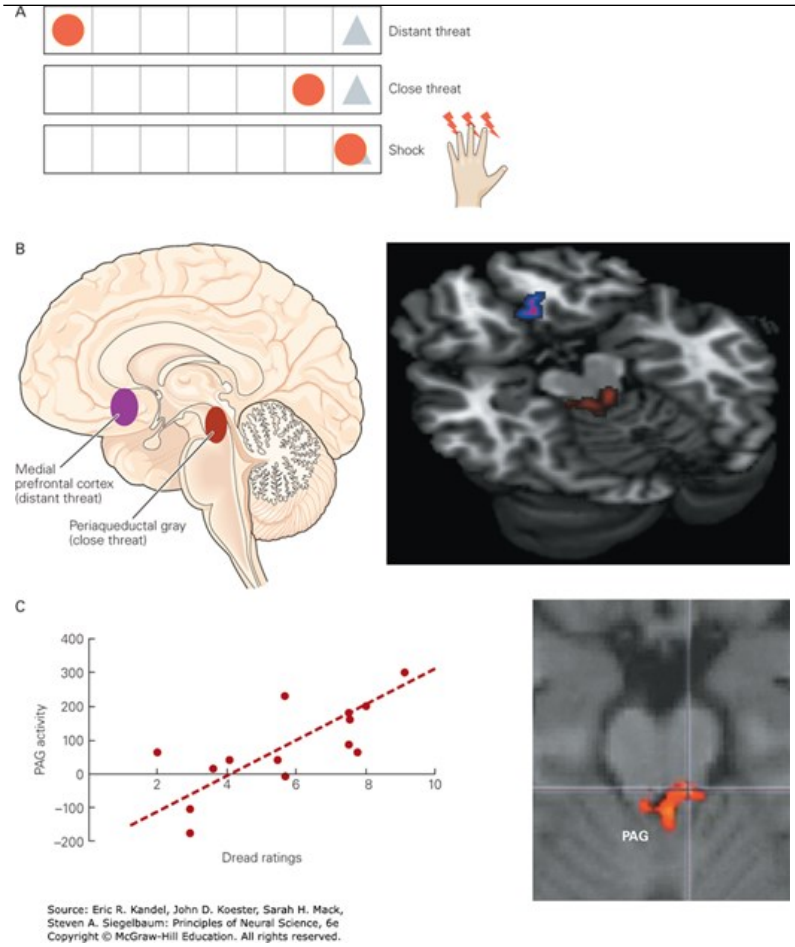
Figure 42–8

Both cortical and subcortical regions come into play during emotion states. Results are from a functional magnetic resonance imaging study in which a subject lies in the scanner while watching a virtual predator (**red dot**) move around on the screen and get closer to a subject (**blue triangle**, representing the actual research participant). (Reproduced, with permission, from Mobbs et al. 2007. Copyright © 2007 AAAS.)

A. Once the predator catches up to the subject, there is a chance that a real and painful electric shock will be delivered to the hand.

B. When the predator gets closer to the subject, activity in the prefrontal cortex and periaqueductal gray matter increases. Notably, this pattern of neural activation shifts such that a distant predator elicits greater activity in the medial prefrontal cortex, whereas a predator close by elicits more activity in the periaqueductal gray.

C. Activation of the periaqueductal gray (**PAG**) is correlated with the subjective sense of dread measured by ratings that subjects gave while in the scanner.



Another brain region of interest in relation to feelings is the subgenual sector of the anterior cingulate cortex (Brodmann's area 25), which has been found in neuroimaging studies to be activated when subjects are experiencing sadness. This region is of special interest because it is also differentially activated in patients with bipolar depression, and it appears thinned in structural MRI scans of patients with chronic depression. Direct electrical stimulation of this brain region (deep brain stimulation) can dramatically improve the mood of some patients with severe depression.

Emotion Is Related to Homeostasis

While it seems clear that no brain region is specialized for any specific emotion, it is even doubtful that there are any brain regions specialized for emotions in general. It may be that all brain regions involved in emotions also carry out other functions. In fact, those nonemotional functions may give us clues about how emotions evolved and, indeed, may be the basic building blocks through which emotion states are assembled.

For example, sectors of the human insular cortex that are activated during recall of feelings are also activated during the conscious sensation of pain and temperature. The insular cortex receives homeostatic information (about temperature and pain, changes in blood pH, carbon dioxide, and oxygen) through pathways that originate in peripheral nerve fibers. These afferent fibers include, for example, the C and Aδ fibers that form synapses with neurons in lamina I of the posterior horn of the spinal cord or the pars caudalis of the trigeminal nerve nucleus in the brain stem. The pathways from lamina I and the trigeminal nucleus project to brain stem nuclei (nucleus of the solitary tract and parabrachial nucleus) and from there to the thalamus and on to the insular cortex. The identification of this functional system is further support for the idea that signals in the afferent somatosensory pathways play a role in the processing of feelings.

Moreover, in patients with pure autonomic failure, a disease in which visceral afferent information is severely compromised, functional imaging studies reveal a blunting of emotional processes *and* attenuation of activity in the somatosensory areas that contribute to feelings. Like other feelings, social feelings engage the insular cortices and the primary and secondary somatosensory cortices (S-I and S-II), as has been found in functional neuroimaging experiments evaluating empathy for pain and, separately, admiration and compassion.

Using these data as support, some influential modern theories build on William James's original hypothesis and propose that the feeling of all emotions is grounded in the brain's representation of bodily homeostasis. As in the case of the amygdala's role in both positive and negative emotions, the insula's role in processing both interoceptive and emotional information is still compatible with the possibility that these processes are distinct. That is, different populations of neurons within these structures may be involved in processing different emotions. Therefore, fMRI may not provide the level of resolution needed to elucidate distinct yet anatomically intermingled neuronal populations, and cellular techniques in animal models may be required.

Although most neuroscience research thus far has focused on negatively valenced emotions, the neural circuitry for positively valenced emotions is being elucidated in studies in both humans and animals. These studies consistently implicate the medial prefrontal cortex in computing the subjective value of rewards, as well as the nucleus accumbens and other nuclei of the basal ganglia in processing the hedonic component (or pleasure) of positive emotions. A growing number of functional imaging studies in humans—especially in the fields of neuroeconomics and social neuroscience—links the role of these structures in emotion processing to their role in value-based decision making and social behavior.

Highlights

1. In the overall physiology of regulating the body and behavior of organisms, emotion states carry out functions intermediate to those of the simpler processes of reflexes and homeostatic regulation, on the one hand, and those of cognitive processes and deliberate behavior on the other. Emotions are more flexible, context-dependent, and controlled than are simple reflexes, but less flexible, context-dependent, and controlled than deliberate behavior. Emotions evolved to produce behavior in response to recurring environmental and internal challenges that are too varied for reflexes, but sufficiently stereotyped that they do not require the full flexibility of cognition.

2. Emotion states need to be carefully distinguished from the conscious experience of emotion (feelings) and also from the concepts and words that we have in everyday language to describe emotions. For example, a hissing cat's behavior is caused by an emotion state, but whether the cat consciously feels afraid is unclear. The cat probably has no concept, and certainly no words, with which to think about the emotion. Human subjects who recognize fear while observing a facial expression are attributing fear to another person and are thinking about a particular emotion, but are not themselves necessarily in a state of fear or experiencing fear. It is a major challenge in designing experiments, especially in humans, to independently control and manipulate these different components of emotion.

3. Emotions coordinate integrated changes in many organismal parameters, including effects on somatic behavior, autonomic and endocrine responses, and cognition. We do not yet understand how this coordination arises, although it is probably achieved through a combination of hierarchical control (through brain regions that function as "command centers" of sorts) and distributed dynamics. Understanding how this is accomplished in biological organisms will also inform how we might engineer robots that exhibit emotional behaviors in the future.

4. Different specific emotions can be thought of categorically (eg, happiness, fear, anger) or dimensionally (in terms of arousal and valence or other dimensional frameworks). It is likely that many of the categories for which we have words in a particular language (like the examples just given) will need to be revised once we have a more scientific understanding. New analytic methods applied to data acquired using fMRI, including methods that take into account the spatial and temporal patterns of brain activity and utilize powerful machine-learning algorithms, may provide new insights into how the brain mediates a broad range of emotions.

5. In humans, emotions can be regulated by several mechanisms. Thus, we have some control over how we feel and some control over how we express emotional behaviors, for instance, through facial expressions. Nonhuman animals do not have this same level of control, and so their emotional behaviors will generally be honest signals of their emotion state, whereas humans often engage in strategic deception.

6. Fear is probably the emotion whose neurobiology is best understood. It depends on the amygdala, in both animals and humans. However, some data suggest that certain types of fear, such as the panic of suffocating induced by inhaling carbon dioxide, are independent of the amygdala. Indeed, we now know that the amygdala is part of a distributed brain system, and therefore, many other brain regions also participate in processing fear. Increasingly, modern studies use sophisticated genetic and cellular techniques to image and to causally manipulate brain function, allowing us to understand the necessary and sufficient roles of multiple brain structures in mediating different emotional behaviors.

7. The ventral and medial prefrontal cortex is intimately involved in emotion and connected with the amygdala. Social emotions, reward representations, and emotion regulation and extinction all involve specific sectors of prefrontal cortex. This region of the brain, together with the

insula, may also be the most important for our conscious experience of emotions, an aspect of emotion that remains the most challenging to study.

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Ralph Adolphs

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