

COMPARING THE EMOTIONAL BRAINS OF HUMANS AND OTHER ANIMALS

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How is emotion embodied in the brain? That is the question posed by affective neuroscience (Cacioppo & Gardner, 1999; Davidson & Sutton, 1995; LeDoux, 1996; Panksepp, 1991, 1998), an enterprise that comprises the efforts of psychologists of emotion and cognition and philosophers of mind, as well as biopsychologists, psychiatrists, neurologists, and other neuroscientists. Affective neuroscience seeks a better understanding of affect and emotion at both psychological and neurobiological levels.

Evidence regarding the brain substrates of feeling and emotion has grown substantially in recent years. But which brain structures are most important for emotion seems to depend to an extent on whom you read. This chapter is intended to address an apparent division in the affective neuroscience literature between views of brain organization that see emotion primarily as a product of the *neocortex* and views that see emotion as a product of *subcortical* brain structures (Figure 3.1). Not at all by coincidence, this corresponds largely to a distinction between those who study emotion and affect in human beings or primates and those who study brain mechanisms of emotion and affect in nonprimate animals.

A newcomer to the affective neuroscience literature would deserve to be forgiven for concluding that there are actually two emotional brains. One literature comes mainly from studies of human subjects, either from PET or fMRI brain imaging of normal individuals or from clinical studies of patients with brain damage. It depicts an emotional brain that is composed chiefly of regions of neo-

cortex. The second literature stresses the role of subcortical systems in emotion and comes chiefly from studies of cats, rats, and other nonprimate animals. These animal studies often involved techniques of brain manipulation (stimulation, lesion, microinjection, etc.) and measured basic behavioral or physiological emotional reactions.

Upon a quick reading one might conclude that there are two different “emotional brains,” depending on which species is being studied. Human and other primate emotion apparently starts at the amygdala and goes upward to the cortex, whereas emotion in most other animals seems to proceed downward from amygdala to the brain stem.

The conclusion that human emotion is cortical but that animal emotion is subcortical would be grossly mistaken, I believe, but it is important to understand why the difference in cortical versus subcortical emphasis has arisen in affective neuroscience. Why have human and animal studies of emotion tended to emphasize different brain structures? And how does the emotional brain of humans really compare to other animals?

I will begin by considering how the two subfields of affective neuroscience differ not only in the species of their subjects but also in their conceptual and methodological approaches. Then a brief review is given of evidence that implicates brain structures from its highest to lowest levels, which suggests that neural mechanisms of affective reaction are highly distributed in both human and animal brains. To understand how the difference in cortical versus subcortical emphases has arisen, we then

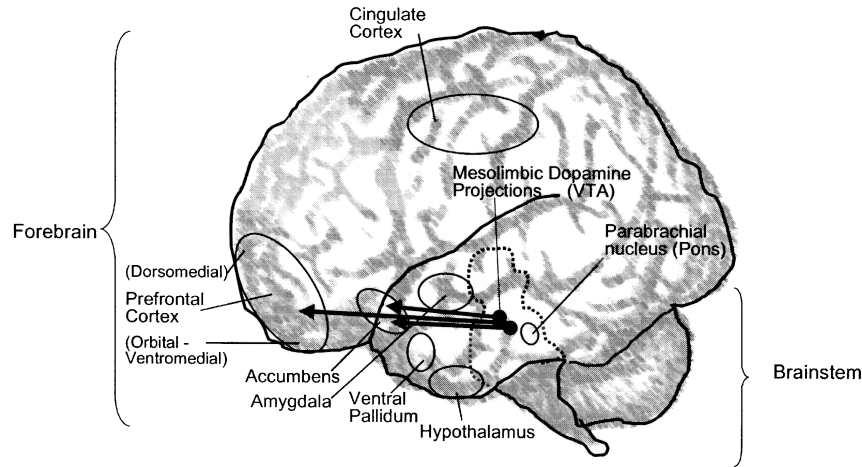


Figure 3.1 Important structures within a generalized emotional brain. The figure shows the placements of each brain structure with respect to front/back and top/bottom, but does not show the relative depth of any structure within the brain. Since the view is from the side, only one of each bilateral pairs of structures can be seen. See text for more detail.

consider various methodological and conceptual artifacts that have exaggerated the perceived difference between humans and other animals. Finally, we examine what real differences in affective neural organization are likely to exist between humans and other animals, and consider the implications of evolutionary encephalization for emotional processing in human brains.

Affective Neuroscience of Humans: Brain Imaging and Brain-Damaged Patients

Most studies in human affective neuroscience either use brain imaging techniques to study normal human subjects or focus on emotional deficits of clinical patients who have suffered focal brain damage. Brain imaging studies include EEG measurements as well as PET or fMRI techniques. All use noninvasive measures to detect changes in large-scale electrical potentials or changes in regional blood flow in brain regions that are correlated to an emotion-related reaction. Human patient studies examine the psychological consequence of brain damage caused by vascular strokes, tumors, surgery, injury, or other disease. The damage is often unilateral, in which case it may be useful for evaluation of hemispheric specialization. For evaluation of the particular role of brain structures, such as prefrontal cortex or amygdala, however, the damage must usually be bilateral. This requirement has generally restricted patient studies to analyses of cortical regions that are often damaged by a single zone of injury, such as frontal, unilateral, or midline cortex areas, or to bilateral zones, such as the temporal lobe that contains the amy-

dala, which are especially vulnerable to selective bilateral injury or to a disease such as epilepsy.

Affective Neuroscience of Animals: Effect of Brain Manipulation of Emotional Reaction

The study of affective neuroscience in nonhuman animals has focused on behavioral and physiological emotional reactions in rodents such as rats, mice, or hamsters, occasionally in cats (though rarely in the past two decades), and in Old World monkeys, such as rhesus macaques. Studies of animals¹ have relied on manipulations of the brain that cause or alter the expression of emotion as much as on measures of neural activity correlated to naturally induced emotion. Common brain manipulation techniques are stereotactically placed lesions (often specific to particular types of neurons in the case of excitotoxin or neurochemical toxin lesions), electrical stimulation, and pharmacological activation or inhibition of neurotransmitter receptors by drugs delivered either systemically or by microinjection into a brain structure. Lesion studies employ a logic similar to that used in studies of brain-damaged humans. Electrical stimulation of the brain can produce the opposite consequence of lesions, exciting neural tissue in the vicinity of the electrode. Pharmacological stimulation provides a more naturalistic way of activating neuronal receptors and is neurochemically selective for neurons with a specific population of neurotransmitter receptors. Pharmacological inhibition by antagonist drugs uses a similar route to produce the opposite effect of receptor suppression. Affective neuroscience stud-

ies of animals also often use techniques to *monitor* neural activity. Electrophysiological measures use surgically implanted microelectrodes to record the neuronal firing patterns of single neurons or groups of neurons. Neurochemical measures, such as microdialysis or voltammetry, detect changes in the extracellular concentration of neurotransmitters. Neuronal metabolism measures, such as c-Fos or c-jun expression in a brain slice collected post-mortem, detect the gene transcription or metabolic activation of internal second messenger systems within neurons, which often accompany sustained changes in functional activation of a neural system.

Limbic System as the Emotional Brain

The term *limbic system* has often been taken to be synonymous with emotional brain. The neuroanatomical term offers a cloak of apparent objectivity. As developed originally by Broca, Papez, and Maclean, the limbic system included both cortical and subcortical structures: cingulate cortex, hippocampus, thalamus, and hypothalamus (Maclean, 1955; Papez, 1937/1995). But the original neuroanatomical definition has not stood the test of time. It was based on what was known prior to 1950 about neural connectivity. Anyone's definition of the emotional brain today would probably include some original structures not on the original list (e.g., amygdala, nucleus accumbens, orbitofrontal cortex) and might remove others from that list. An excellent history and cogent critique of the limbic system as a neuroanatomical concept has been provided by LeDoux (1996), who suggests the label limbic system is too flawed to be of future use. He argues that the emotional brain cannot be predefined on the basis of anatomical connections. Instead, he argues that the emotional brain can be identified only by functional studies—that is, studies that provide actual neurobehavioral evidence that a brain structure mediates some aspect of emotion.

LeDoux's criticisms of the limbic system as a neuroanatomical entity are undoubtedly right, and I believe he is correct to insist that the emotional brain can be identified only by functional studies. But although it would be more direct to simply say "emotional brain," the term *limbic system* will probably not fade from use. It is far too entrenched in current usage to be rooted out, and the apparent objectivity of its neuroanatomical concreteness—even if illusory—remains too powerfully attractive for neuroscientists to abandon it. It will forever be preferred by a group of investigators that is uncomfortable talking explicitly about emotional functions because it views terms of emotion as insufficiently concrete to serve as scientific labels and seeks an objective fig leaf. That the fig leaf is only an illusion in the mind of the wearer does not at all diminish the comfort it affords. This practice may not be entirely bad, however, since use of "limbic" (rather than,

say, the "fear brain") avoids the danger of identifying brain structures too closely with interim concepts of emotion, when either the identification or the concepts may turn out eventually to need modification. Still, both the emotions and the brain structures that mediate them must be identified by the empirical results of functional neurobehavioral studies. Even if we use the term *limbic system*, it must be defined based on functional evidence that a particular brain stem truly mediates a particular emotional process. Functional evidence reigns in deciding issues of this type. So what is the current functional evidence on the emotional or limbic brain?

Review of Brain Structures in Emotion

Orbitofrontal Cortex (Prefrontal Cortex)

Prefrontal cortex lies at the very front of the brain.² The ventral or bottom one-third of prefrontal cortex is called the orbitofrontal cortex, a name that derives from its position immediately above the eyes or orbits. Orbitofrontal cortex is most elaborately developed in humans and other primates, though it is present to some extent in all mammals. In his recent book on brain systems of emotion, Rolls writes concerning its role that "especially important for reward and punishment, emotion and motivation, are the orbitofrontal cortex and amygdala, where primary reinforcers are represented. These parts of the brain appear to be especially important in emotion and motivation not only because they are the parts of the brain where in primates the primary (unlearned) reinforcing value of stimuli is represented, but also because they are the parts of the brain that perform pattern-association learning between potential secondary reinforcers and primary reinforcers. They are thus the parts of the brain involved in learning the emotional and motivational value of stimuli" (Rolls, 1999, pp. 286–287).

In his popular and thoughtful books on human brain function, Damasio also singles out the orbital or ventromedial prefrontal cortex for special importance regarding emotion (Damasio, 1994, 1999). For example, "Primary emotions (read: innate, preorganized, Jamesian) depend on limbic system circuitry, the amygdala and anterior cingulate being the prime players. . . . But the mechanism of primary emotions does not describe the full range of emotional behaviors. . . . The network must be broadened, and it requires the agency of prefrontal and of somatosensory cortices" (Damasio, 1994, pp. 133–134).

For both Rolls and Damasio the neocortex, and especially the prefrontal cortex, is the emotional apex of the brain. Rolls's view is based on 25 years of important electrophysiological studies by him and his colleagues of orbitofrontal neurons in monkeys that have received rewards or associated stimuli. They have shown that

orbitofrontal neurons fire vigorously when a monkey tastes a favorite food or when it sees the food or an associated stimulus (as do neurons in hypothalamus and amygdala; Rolls, 1997, 2000; Rolls & Baylis, 1994; Rolls, Critchley, Browning, Hernadi, & Leonard, 1999; Rolls, Yaxley, & Sienkiewicz, 1990). Orbitofrontal cortex neurons, these studies find, respond especially to the hedonic or affective reward properties of the taste or to the sight of the learned stimulus that predicts those reward properties. Most especially, if the predictive reward value of a learned stimulus is switched back and forth, orbitofrontal neurons uniquely track the switch and change their response to follow the current reward-signaling status of the stimulus (Rolls, 2000; Rolls, Scott, Sienkiewicz, & Yaxley, 1988). Also, if the monkey is allowed to eat its fill of a particular delicious food, orbitofrontal neurons cease firing to its sight or smell, showing a neural decrement that correlates to the food's diminished hedonic value (Rolls et al., 1988). Most "reward neurons" in other regions of the brain, by contrast, remain constant in response to the same situation, coding the "sensory quality" of the taste rather than the "affective quality," though hypothalamus and amygdala may also be affective exceptions (Rolls, 1999; Yan & Scott, 1996). When humans eat a food to repletion, the palatability or pleasure they report to further tastes of the food diminishes (Cabanac, 1979), and the decline in orbitofrontal neuron firing presumably reflects a related decrease in hedonic impact for the monkey.

Brain imaging PET and fMRI studies of normal human subjects have found changes in orbitofrontal cortex in response to pleasant or unpleasant tastes (Zald, Lee, Fluegel, & Pardo, 1998) and odors (Francis et al., 1999; Zald & Pardo, 1997) (although not all studies have found orbitofrontal changes in response to pleasant/unpleasant odors [Fulbright et al., 1998]). Similarly, human orbitofrontal activation has been found to pleasant touch (Francis et al., 1999), and even to pleasant music (Blood, Zatorre, Bermudez, & Evans, 1999) or to a monetary reward (Thut et al., 1997). Changes in human prefrontal cortex (containing orbitofrontal cortex) have also been reported to be evoked by traumatic photographs in former soldiers who suffered from posttraumatic stress disorder (Bremner et al., 1999; actually this study showed a *decrease* in PET measured blood flow during the emotion, but the relation of blood flow to neuronal or neurochemical activation is complex).

Basic rewarding stimuli such as cocaine or similar drugs also produce changes in human orbitofrontal cortex. Orbitofrontal responses have been found in humans to cocaine, opiates, and THC (the active ingredient in marijuana), especially in regular abusers (Breiter et al., 1997; Firestone et al., 1996; Volkow et al., 1996). Even stimuli associated with cocaine use, which evokes feelings of craving in addicts, may activate the prefrontal cortex (Maas et al., 1998), though not in all studies (Childress et al., 1999).

Most of the focus on the prefrontal cortex has come from studies of humans or monkeys, but other animals show prefrontal responses to emotional events too (Kolb & Tees, 1990). In rats, prefrontal cortex neurons have been shown to fire action potentials in response to cocaine or heroin (Chang, Janak, & Woodward, 1998) or in response to an odor that signals a reward (Schoenbaum, Chiba, & Gallagher, 1999). Rats will also work to administer a microinjection of cocaine or related drugs directly into their medial prefrontal cortex (Carlezon & Wise, 1996; Goeders & Smith, 1983). There are even neuroanatomical changes induced in the structure of dendrites on neurons in prefrontal cortex of rats after exposure to addictive drugs that produce neurobehavioral sensitization (Robinson & Kolb, 1997, 1999).

Neurochemical release of dopamine in the prefrontal cortex of rats, measured by microdialysis or in vivo voltammetry, occurs when a rat eats an especially palatable food (Bassareo & DiChiara, 1997) or when it works for a food reward (Richardson & Gratton, 1998). Expression of "immediate early gene" markers such as Fos protein, indicating rapid transcription of the c-Fos gene and probable metabolic activation of the neuron, is triggered in rat prefrontal cortex by rewarding electrical brain stimulation of the hypothalamus (Hunt & McGregor, 1998). Unpleasant shocks or other stressful events also elicit dopamine release in the prefrontal cortex of rats, as do associated stimuli that predict those stressful events (Davis et al., 1994; Yoshioka, Matsumoto, Togashi, & Saito, 1996). Thus, in humans, monkeys, and rats, affective stimuli are powerful elicitors of neural activation in prefrontal and orbitofrontal cortex.

What are the emotional consequences of losing orbitofrontal or entire prefrontal cortex? The answer to this is crucial for interpreting whether or not prefrontal cortex activation is truly a neural apex for emotion. Is orbitofrontal or other prefrontal cortex *necessary for causation of the emotion* triggered by affective events? If so, then loss of prefrontal cortex should disrupt the capacity for most emotional experiences and responses. However, the consequence of prefrontal cortex loss appears to be far more subtle than a loss of emotion. This is our first clue that prefrontal cortex plays a different causal role than to "mediate" emotion in a simple direct sense.

Rolls (1999, p. 115) writes that "in the human, euphoria, irresponsibility, and lack of affect can follow frontal lobe damage" (see Kolb & Whishaw, 1990; Damasio, 1994; Eslinger & Damasio, 1985), particularly orbitofrontal damage" (Rolls, Hornak, Wade, & McGrath, 1994a). Lack of affect is indeed what one might expect if the capacity for emotion were eliminated, though it is somewhat contradicted by the listing of euphoria as another consequence.

The paradox between euphoria versus flattened affect after damage to prefrontal cortex may be partly resolved by distinguishing subregions within it (Cummings, 1995;

Tucker, Luu, & Pribram, 1995). Lack of affect and general apathy are most often reported after damage to the dorsal region, especially to dorsomedial prefrontal cortex. Euphoria, impulsiveness, and general emotional disinhibition appears to be more commonly a consequence of damage to the ventral region, especially ventromedial and orbital prefrontal cortex (Tucker et al., 1995). Some neuroanatomists argue further that among ventral prefrontal cortex, the ventromedial region can be distinguished anatomically from the orbital region on the basis of connections with other structures, a distinction that appears to apply to monkeys and rats as well as to humans (Kolb & Tees, 1990; Ongur & Price, 2000). For example, taste and smell inputs appear to go most directly to the orbital region, whereas outputs to the nucleus accumbens originate primarily in the ventromedial region (Ongur & Price, 2000).

But how important is prefrontal cortex to the actual *causation* of an emotion? If by lack of affect is meant the utter loss of affective reactions, then that appears to be extremely rare and perhaps nonexistent in humans after prefrontal damage (Damasio, 1994, 1996). All prefrontal lesion patients still seek some simple pleasures: they choose palatable foods and eat them (and may even overeat); they react to some pains and avoid some unpleasant events; and they may become angry, or fearful, or sexually aroused in certain situations. Though their behavior regarding emotional events may be unquestionably odd in certain respects, it would clearly be an exaggeration to say that they have lost all emotion or are incapable of affective reaction (Damasio, 1994, 1996; Valenstein, 1986).

Animals, too, after prefrontal lesions react affectively to many emotional stimuli, even if their reactions are sometimes blunted or misdirected. Rolls writes (1999, p. 115) that rhesus monkeys after prefrontal lesions have “reduced aggression to humans and to stimuli such as a snake and a doll, a reduced tendency to reject foods such as meat [Butter, McDonald, & Snyder, 1969; Butter & Snyder, 1972; Butter, Snyder, & McDonald, 1970], and a failure to display the normal preference rankings for different foods” (Baylis & Gaffan, 1991). These emotional deficits seem relatively subtle, compared to the possibility of losing all emotion that might be expected if the prefrontal cortex were the chief site “where primary reinforcers are represented.”

In a fascinating study of human patients after loss of the prefrontal cortex, Bechara and colleagues (Bechara, Damasio, Tranel, & Damasio, 1997) asked prefrontal patients to play a card game in which they could win or lose a reward, and in which they had to figure out the best strategy for winning on their own as they went along. Bechara and colleagues found that prefrontal patients were eventually able to figure out the strategy for winning of the game and to describe it explicitly, but they had several deficits. First, while normal subjects seemed to absorb and

use the inferred strategy in relatively early trials, guided by hunches they could not explain even before they were able to explicitly describe what that strategy was, prefrontal patients were not able to follow these “nonconscious biases” prior to being able to describe the strategy. Second, even after they were able to explicitly describe the strategy, prefrontal patients sometimes still failed to follow it in their playing, and made unwise decisions and incurred losses even though in one sense they “knew” and could say what the best strategy was. From neuropsychological tests, such as the Wisconsin card-sorting task, prefrontal lesions are famous for inducing such perseverative errors (especially dorsolateral prefrontal lesions), such as continuing to employ a choice strategy even after it becomes wrong and a different strategy is called for—and even if the patient knows and can say that it is wrong (Hauser, 1999; Kolb & Whishaw, 1996). Finally, prefrontal patients had blunted autonomic skin conductance responses to outcomes while playing the game. In particular, they failed to show a skin conductance response when they played strategies that produced losses, in advance of the loss itself, unlike normal subjects who showed the autonomic response and may have used it as a cue to guide subsequent action (Bechara et al., 1997).

Damasio and colleagues interpret the lack of such anticipatory autonomic emotional reactions to loss to mean that prefrontal patients are unable to generate or to follow “somatic markers” that label emotional outcomes, and so the patients fail to devise and follow the strategies based on emotional outcome that often guide normal human behavior (Bechara, Damasio, & Damasio, 2000; Bechara et al., 1997; Damasio, 1994, 1996, 1998). Somatic markers, according to Damasio, are physiological reactions, such as the skin conductance response, often generated to an emotional event without conscious awareness (a view of affective reaction similar to that suggested by Zajonc [1980, 1998]). Damasio and colleagues suggest these reactions may function as crucial informational cues for further action. They may possibly influence the final conscious experience of the emotion (in a sense similar to the classic James-Lange hypothesis, in that they may cause sensations that are felt as part of the conscious emotion; James, 1884), but more certainly are posited to guide or trigger behavioral strategies on the basis of the emotion. It is the failure to use somatic markers, Damasio suggests, that makes prefrontal patients unable to benefit from normal “nonconscious biases” that provide useful hunches and that makes them choose wrongly even after they explicitly understand the rules (Bechara et al., 1997; Damasio, 1994, 1996, 1998).

The “somatic marker” hypothesis of emotion offered by Damasio and colleagues is remarkable in part for its specificity regarding the role of prefrontal cortex in emotion. This role is very different from a general loss of primary or even secondary emotion and is much more circum-

scribed than emotional loss. After loss of prefrontal cortex, people may fail to generate some emotional reactions and may fail in some way to incorporate the emotional consequences of their own actions into their everyday behavioral strategies. But they do not lose all capacity for affective reaction, they are not missing all primary emotions or any particular emotion, and they do not even lack capacity for learning emotion. They are still emotional creatures in virtually every sense—just, sometimes and in subtle ways, slightly odd in the way they act on their emotions.

An intriguing and related hypothesis has been suggested for prefrontal cortex—namely, that *emotional regulation* may be the psychological function most impaired (Davidson, Jackson, & Kalin, 2000; Tucker et al., 1995). Emotional regulation means to exercise deliberate voluntary control over the magnitude of an emotional or affective reaction. This can mean either to deliberately suppress an emotional reaction that might otherwise occur, or to deliberately induce an emotion in oneself by cognitive means (Davidson et al., 2000; Tucker et al., 1995). It has even been suggested that suppression versus induction types of emotional regulation might be mediated by different prefrontal regions, such that euphoria after ventral or orbital damage could reflect lack of regulatory suppression of emotional reaction, whereas lack of affect after dorsomedial damage could reflect loss of regulatory induction of emotion (Tucker et al., 1995). As yet, little experimental evidence exists concerning the role of prefrontal cortex in emotional regulation, although one promising approach has begun to compare cortical activity during voluntary changes in emotional reaction to that during spontaneously induced emotion (Davidson et al., 2000).

Cingulate Cortex

Cingulate cortex consists of a longitudinal strip running front to back along the midline on each hemisphere of the brain. The anterior or front region of this strip is especially implicated in human emotion, as alluded to in the quote above from Damasio, and cingulate cortex has been implicated in human clinical conditions such as depression, anxiety, and other distressing states (Davidson, Abercrombie, Nitschke, & Putnam, 1999).

Pain and distress in many forms have been linked to cingulate cortex by PET and fMRI brain imaging studies (Davis, Taylor, Crawley, Wood, & Mikulis, 1997; Porro, Cettolo, Francescato, & Baraldi, 1998; Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Tolle et al., 1999). Even the mere anticipation of pain may produce fMRI activation of (right) anterior cingulate cortex (Hsieh, Stone-Elander, & Ingvar, 1999). *Reduction* of pain via opiate fentanyl anesthesia has also been suggested to *increase* PET signal in cingulate cortex, somewhat paradoxically, even though it decreases the subjective conscious experience of the pain that by itself seems to produce cingulate activation (Adler

et al., 1997). Nitrous oxide anesthesia, by contrast, may abolish the cingulate PET response to pain (Gyulai, Firestone, Mintun, & Winter, 1997). Clearly, the neural encoding of pain and anesthesia must be complex, and the full story remains to be understood.

Analgesia induced by hypnosis has been reported to reduce the electrical potential evoked from human cingulate cortex by a painful skin stimulus (Kropotov, Crawford, & Polyakov, 1997). A favored neurosurgical approach to the treatment of intractable pain in human patients has long been surgical destruction of the cingulate cortex, and this appears effective often (Hurt & Ballantine, 1974; Kondziolka, 1999). For reasons that are less clear, cingulate cortex lesions have also been favored for a variety of other human psychological disorders such as depression and obsessive-compulsive disorder (Hay et al., 1993; Hay & Sachdev, 1992; Valenstein, 1986). Remarkably, cingulate cortex lesions have even been suggested as a possible psychosurgical “treatment” for human sex offenders (Brown, 1995), although the impaired ability to inhibit nonreward responses that follow cingulate cortex lesions in animals (below) raises the question as to whether cingulate lesions might instead exacerbate some sexual offences. It is worth noting that prescriptive psychosurgery applied to criminal or antisocial behavior in humans has had a very poor record in the past (Valenstein, 1974, 1986).

Brain imaging studies of cingulate cortex in other emotional situations have produced results similar to orbitofrontal or prefrontal cortex. Affectively rewarding drugs like cocaine, fentanyl, or marijuana’s THC produced increased fMRI blood flow signal in cingulate when given intravenously (Breiter et al., 1997; Firestone et al., 1996; Mathew, Wilson, Coleman, Turkington, & DeGrado, 1997), though cingulate cortex was also activated by procaine HCl infusions that triggered panic attacks that were unpleasant (Servan-Schreiber, Perlstein, Cohen, & Mintun, 1998). Even mere craving for cocaine, induced by photographs of drug use, appears to produce cingulate activation in human drug addicts (Childress et al., 1999; Maas et al., 1998). Induction of sexual arousal or of competitive arousal, in men at least, also has been linked in one PET study to increased blood flow in anterior cingulate cortex (Rauch et al., 1999).

Transient sadness and clinical depression both have been associated with cingulate fMRI activation (Mayberg et al., 1999). Gustatory distaste for an unpleasant concentrated salt solution also activates cingulate cortex (Zald et al., 1998), and the cingulate cortex was the structure that showed the strongest PET signal in humans experiencing sensations of thirst (Denton et al., 1999).

There are intriguing suggestions that the recognition of emotional facial expression may involve cingulate cortex. Captioned photographs of both positive and negative emotional scenes produced fMRI activation in the right cingulate cortex, possibly with a special advantage for nega-

tive scenes (Teasdale et al., 1999). However, no special cingulate involvement was found to sad faces in a study of expression recognition, though happy faces produced left sided cingulate activation (Phillips et al., 1998). The laterality of these reported effects is consistent with Davidson's suggestion of left-hemisphere specialization for positive emotion, and right-hemisphere specialization for negative emotion, discussed below (Davidson, 1998a; Davidson & Sutton, 1995; Sutton & Davidson, 1997).

Although human subjects constitute the main source for a role of cingulate cortex in emotion, studies of rats also provide evidence for cingulate cortex activation in emotional situations. The c-Fos marker of neuronal activation is increased in cingulate cortex of rats that fear an impending electric shock (Beck & Fibiger, 1995). In positive emotional situations, cingulate cortex lesions in rats are reported to result in an increase in responses to a non-rewarded stimulus (Bussey, Everitt, & Robbins, 1997) and to increase perseverative responses to no-longer rewarded maze choice (Seamans, Floresco, & Phillips, 1995).

Amygdala

The amygdala is one of the best known structures in animal and human affective neuroscience and features prominently in most brain-referenced theories of emotion (Cacioppo, Gardner, & Berntson, 1999; Damasio, 1994; Davidson et al., 1999; Gallagher & Chiba, 1996; Gray & McNaughton, 1996; Kagan & Schulkin, 1995; LeDoux, 1996; Panksepp, 1998; Rolls, 1999; Schulkin, 1994; Toates, 1994; Zajonc, 1998).

Kagan, Schulkin, and others have posited human anxiety disorders to be modulated by chronic hyperactivity in the amygdala (Kagan & Snidman, 1991; Schulkin, 1994; Schwartz, Snidman, & Kagan, 1996). In brain-imaging studies, human subjects who experienced an unpleasant taste or odor showed changes in PET signal in amygdala (Zald et al., 1998; Zald & Pardo, 1997), as did subjects who experienced intense feelings of thirst (Denton et al., 1999). The visual perception of an angry or fearful face also has been reported to trigger changes in blood flow to human amygdala (Baird et al., 1999; Phillips et al., 1997), though another PET study reported amygdala activation after visual perception of sad facial expressions but not of angry expressions (Blair, Morris, Frith, Perrett, & Dolan, 1999). In some cases, the amygdala change may occur even if the face is seen too briefly to be consciously perceived (i.e., in a subliminal priming paradigm; Morris, Ohman, & Dolan, 1998). Emotionally unpleasant photographs of other types also have been reported to elicit amygdala PET changes (Lane et al., 1997). Classical conditioning of responses to particular faces, induced by pairing neutral facial expressions with an unpleasant odor, induced suppression of fMRI signal in amygdala of normal subjects,

but an increase in signal in patients with social phobias (Schneider et al., 1999).

Adolphs and colleagues found that a human patient who had bilateral lesions of the amygdala showed impaired recognition of emotional facial expression, especially for fearful expressions (Adolphs, Tranel, Damasio, & Damasio, 1994; Adolphs, Tranel, Damasio, & Damasio, 1995). Similarly, auditory recognition of fear expressed by a human voice has been reported to be impaired after amygdala lesions (Scott et al., 1997). However, another study found normal recognition of vocal expression of fear in a patient with bilateral amygdala damaged, and suggested that deficits of auditory emotional recognition may actually be due to damage to basal ganglia (i.e., caudate-putamen or neostriatum) rather than to amygdala (Anderson & Phelps, 1998).

In rats, conditioned fear and anxiety reactions have long been known to depend on the amygdala (Davis, 1992; Fanselow & LeDoux, 1999; Gallagher & Chiba, 1996; LeDoux, 1996, 1992; Maren & Fanselow, 1996). In the literature on animal amygdala, a distinction is often made between subregions of the amygdala. In particular, the basolateral nucleus of the amygdala lies at the bottom outside edge of the amygdala on both sides, whereas the central nucleus of the amygdala lies slightly above and nearer the middle of the brain. The basolateral nucleus of the amygdala receives many sensory inputs from other brain structures, and it projects chiefly to the central nucleus of the amygdala in turn. This arrangement allows information to be processed in a serial fashion, first in basolateral nucleus and then in central nucleus (Fanselow & LeDoux, 1999; LeDoux, 1998; Maren, 1999a). However, there also exist some direct sensory inputs from other brain structures to amygdala central nucleus, which bypass the basolateral nucleus and direct outputs from basolateral nucleus to other brain structures, which bypass the central nucleus, and these pathways allow for the possibility of independent or parallel processing too (Everitt, Cardinal, Hall, Parkinson, & Robbins, 2000; Killcross, Robbins, & Everitt, 1997; Parkinson, Robbins, & Everitt, 2000). The relative roles of basolateral and central amygdala subregions in emotion is currently a topic of much research in animal affective neuroscience.

Lesions of the basolateral or central amygdala in rats often disrupt the acquisition of new conditioned fears, as well as the expression of "old" fears conditioned to previously trained sounds or places (Davis, 1992; Fanselow & LeDoux, 1999; Killcross et al., 1997; LeDoux, 1996; Maren & Fanselow, 1996). However, some investigators have suggested that basolateral amygdala and central amygdala play different roles in fear learning and that lesions of the two nuclei may disrupt different types of learned fear responses (Killcross et al., 1997).

Amygdala lesions alter many reactions of animals to emotionally *positive* events as well, as has been apparent

since the Kluver and Bucy's original report of hyperorality and hypersexuality in monkeys (Kluver & Bucy, 1939). Reaction to primary rewards is altered in other species as well. For example, rats fail to work for a salty reward when they are in a physiological state of sodium depletion (Schulkin, 1991; Schulkin, Marini, & Epstein, 1989) and fail to consume salt that is freely given after amygdala lesions, even though they emit normal positive hedonic reactions to a salty taste if it is put into their mouths (Galaverna et al., 1993; Schulkin, 1991; Seeley, Galaverna, Schulkin, Epstein, & Grill, 1993).

Everitt and Robbins and their colleagues have suggested aspects of reward *learning* to be especially disrupted by amygdala damage (Everitt et al., 2000; Everitt & Robbins, 1992; Parkinson et al., 2000). For example, male rats fail to perform a learned task to earn access to a sexual partner after amygdala damage, even though the same rats will engage in copulation if access to the female is freely granted (Everitt, 1990). Similarly, in a "conditioned reinforcement" task, lesions of the basolateral amygdala appear to reduce the value of learned rewards to rats. Ordinary rats will work for conditioned stimulus (a light or sound) that has been paired either with food or with a sexual partner, but amygdala lesions eliminate such "conditioned reinforcement" and disrupt some other appetitive learned responses (though the rats will still work for food reward itself; Everitt, 1990; Everitt et al., 2000; Everitt & Robbins, 1992; Parkinson et al., 2000).

The parenthetical caveat above signifies that destruction of the amygdala is clearly not sufficient to eliminate all reward or emotional learning, as there is much evidence that aspects of learned reward and learned fear persist after amygdala destruction. For example, monkeys still show fear to especially strong stimuli after bilateral amygdala lesions (Kling & Brothers, 1992), even though the original Kluver-Bucy syndrome emphasized the taming of monkeys and apparent elimination of fear in some situations (Kluver & Bucy, 1939). Many of the deficits of conditioned fear or conditioned reward produced by damage to the amygdala appear to be specific to a particular *type* of fearful or reward stimulus or to a particular task or measure of fear or reward learning (Everitt & Robbins, 1992; Hatfield, Han, Conley, Gallagher, & Holland, 1996; Kim & Davis, 1993; Pesold & Treit, 1995; Treit, Pesold, & Rotzinger, 1993).

Perhaps the most "typical" deficit after amygdala damage is the loss of Pavlovian conditioned fear responses such as freezing or startle in response to a shock paired sound. Pavlovian fear learning is considered by some to be a chief emotional function carried out by amygdala systems (Davis & Lee, 1998; Fanselow & LeDoux, 1999; LeDoux, 1996; Maren, 1999a). But even the "lost" capacity to learn some Pavlovian conditioned fear reactions may reemerge to relatively normal levels after central or baso-

lateral amygdala lesions if rats are given many additional learning trials (Kim & Davis, 1993; Maren, 1999b), suggesting that fear learning is not lost but merely very slowed after the lesion. And a human patient who is unable to categorize the visual perception of a fearful facial expression may nonetheless recognize fear in verbal descriptions and even be able to produce excellent voluntary facial expressions of fear herself (Anderson & Phelps, 2000). Whether any particular type of fear learning or other psychological category of emotional learning or emotional reaction will eventually be found to be totally disrupted by amygdala lesions remains at present an open question.

An alternative view is that amygdala lesions do not eliminate any learned emotions or affective reactions of any type (Berridge, 1999; Gallagher & Holland, 1994; Weiskrantz, 1997). Instead, they appear to disturb a *targeting* of affective reaction to particular stimuli. As Weiskrantz (1956) put it in an early and perspicacious observation, what amygdala lesions appear to do is to disrupt an aspect of the "emotional significance of perceived stimuli." That may not be the same as disruption of emotion itself. The motivational targeting function would be instead a *nonaffective* process that controls the *triggering* of reward, fear, and other motivational and emotional processes by particular stimuli. The targeting function has been suggested by some to be an attentional mechanism that gates information processing (Gallagher & Holland, 1994) or to be an incentive salience assignment mechanism that attaches motivational significance to the perception of particular stimuli (Berridge, 1999). However, a complete account has not yet been formulated in terms of either of these frameworks, nor in terms of emotion (fear, reward, etc.), associative learning, or of emotional learning, which can satisfactorily account for the deficits that result from amygdala damage (see also Aggleton, 2000, and pp. 547–553 in Berridge, 1999). It remains a challenge for affective neuroscience to produce a proper characterization of the role of amygdala nuclei in fear and in other emotion.

Accumbens and Mesolimbic Dopamine and Opioid Systems

The nucleus accumbens, which lies at the front of subcortical forebrain and is rich in dopamine and opioid neurotransmitter systems, is a brain structure as famous for *positive* affective states as the amygdala is for fear. Accumbens systems are often portrayed as reward and pleasure systems. Activation of dopamine projections to the accumbens and related targets has been viewed by many neuroscientists as a neural "common currency" for reward (Koob & Le Moal, 1997; Panksepp, 1998; Phillips, Blaha, Pfau, & Blackburn, 1992; Rolls, 1999; Shizgal, 1997;

Wise, 1996). For example, Shizgal calls the neural system constituted by these brain structures an “affective channel” for positive reward (Shizgal, 1999).

Drugs, rather than lesions, have often been used to study the affective consequences of suppression or activation of accumbens-related dopamine and opioid systems (Koob & Le Moal, 1997). The simple social fact that billions of human beings have chosen to stimulate their own mesolimbic systems via the ingestion of drugs, beginning thousands of year ago with alcohol and opiates and continuing today with a vast array of natural and synthetic compounds, constitutes a kind of voluntary experiment by generations of human subjects whose results support a causal role of this brain system in positive emotion (Nesse & Berridge, 1997).

Dopamine (especially dopamine projections to accumbens) has often been called the “brain’s pleasure neurotransmitter” (Nash, 1997; Pani & Gessa, 1997; Wickelgren, 1997; Wise, 1985). In rats, electrophysiological or neurochemical studies of accumbens neuronal activity or dopamine release have shown this neural system to be activated by many pleasant rewards. For example, accumbens activation and dopamine release occur in response to palatable food (Apicella, Ljungberg, Scarnati, & Schultz, 1991; Blackburn, Phillips, Jakubovic, & Fibiger, 1989; Richardson & Gratton, 1996; Schultz, Dayan, & Montague, 1997), to rewards such as heroin or amphetamine (Kiyatkin, Wise, & Gratton, 1993; Ranaldi, Pocock, Zereik, & Wise, 1999), and to the chance to engage in sexual copulation in both females and males (Fiorino, Coury, & Phillips, 1997; Mermelstein & Becker, 1995; Pfaus, Damsma, Wenkstern, & Fibiger, 1995). Accumbens activation and dopamine release are also elicited by secondary rewards, such as conditioned stimuli that have been paired with food, drugs, or sex (Apicella et al., 1991; Di Ciano, Blaha, & Phillips, 1998; Hoebel, Mark, & West, 1992; Hollerman, Tremblay, & Schultz, 1998; Kiyatkin & Gratton, 1994).

Rewarding electrical brain stimulation (typically delivered via hypothalamic electrodes) may be a related reward mediated by this system, though in some ways it is more difficult to interpret. Brain stimulation reward has long been viewed as mediated by mesoaccumbens dopamine systems (Gallistel, Boytim, Gomita, & Klebanoff, 1982; Phillips & Fibiger, 1973; Shizgal, 1997; Wise, 1998). However, direct measures indicate only weak neuronal activation of dopamine projections by electrical stimulation (Gallistel, 1986; Garris et al., 1999; Hunt & McGregor, 1998). Conversely, drugs that block dopamine receptors were once suggested to produce anhedonia (Wise, 1985), and certainly those drugs reduce some aspect of reward, as they decrease the willingness of animals to work for food rewards (Blackburn, Phillips, & Fibiger, 1987; Ettenberg & Camp, 1986; Salamone, Cousins, & Snyder, 1997; Smith, 1995; Wise, Spindler, deWit, & Gerberg, 1978), ad-

dictive drug rewards (De Wit & Wise, 1977; McFarland & Ettenberg, 1998; Roberts, Loh, & Vickers, 1989), and electrical brain stimulation rewards (Fouriez & Wise, 1976; Gallistel & Karras, 1984; Nakajima & Patterson, 1997; Wise, 1991), among other reward-related effects.

In human imaging studies of accumbens or of dopamine projections, signal activation has been reported to be produced by many types of rewarding drugs of abuse that human addicts commonly take, including amphetamine, heroin, cocaine, and fentanyl (Breiter et al., 1997; Firestone et al., 1996; Sell et al., 1999; Vollenweider, Maguire, Leenders, Mathys, & Angst, 1998). Even mere craving for these drugs, induced by looking at photographs of people taking drugs, appears to modulate these neural systems (Childress et al., 1999; Sell et al., 1999). Purely psychological human recreations also appear to activate dopamine systems in the nucleus accumbens and related structures (sometimes called ventral striatum in humans). For example, human subjects in a PET study played a tank battle videogame in which they won money whenever they collected flags or destroyed the enemy tanks, and players showed an increase in the amount of dopamine released in their nucleus accumbens (indicated by a decrease in the binding of a radioactive drug to dopamine receptors, because extra dopamine presumably displaced the drug from the receptors; Koeppe et al., 1998). Regarding this observation, the authors wrote: “We interpret changes in ventral striatal [11C] RAC binding to be related to affective components of the task” (Koeppe et al., 1998, p. 267).

My colleagues and I have conducted a number of studies in rats on the role of dopamine in hedonic impact over the past decade, guided at first by the hypothesis that “dopamine = hedonia” (Gardner & Lowinson, 1993; Wise, 1985). We have measured behavioral affective reactions of rats to food reward, which are related to the facial expressions that human babies show to sweet tastes (Steiner, 1973; Steiner, Glaser, Hawilo, & Berridge, 2001). Those positive affective reactions provide a specific behavioral measure of the *hedonic impact* of a taste (Berridge, 2000). We originally expected to find that manipulations that suppressed dopamine neurotransmission would impair the hedonic impact of food rewards and suppress positive affective reactions to a sweet taste. Therefore, we were surprised to find that dopamine did not seem necessary for normal hedonic reaction to the reward property of sweet tastes. Neither anti-dopamine drugs nor massive 6-OHDA lesions of dopamine neurons impaired hedonic impact, as expressed by affective reactions (Berridge & Robinson, 1998; Berridge, Venier, & Robinson, 1989; Peciña, Berridge, & Parker, 1997).

That was puzzling because it seems quite clear that dopamine is needed for *some* aspect of reward (Panksepp, 1998; Rolls, 1999; Shizgal, 1997; Smith, 1995; Wise, 1982;

Wise, 1985). To help resolve the puzzle, my colleagues and I suggested that incentive salience or “wanting” for rewards better captures the psychological aspect of reward contributed by dopamine, rather than pleasure, hedonic impact, or “liking” for the same rewards (see Berridge & Robinson, 1998, for review). Consistent with our hypothesis that “dopamine is needed for wanting but not liking” are recent reports that suppression of dopamine neurotransmission in humans who take a pleasurable drug, such as amphetamine or cocaine, does not suppress their reported drug pleasure, even when it reduces their drug craving (Brauer & De Wit, 1997; Brauer, Goudie, & de Wit, 1997). Finally, I should also mention that dopamine accumbens systems are activated in aversive situations such as when rats expect or receive foot shock or other stressors (Gray et al., 1997; Rada, Mark, & Hoebel, 1998; Salamone, 1994; Young, Ahier, Upton, Joseph, & Gray, 1998). The psychological implications of this joint participation in positive and negative motivational states are complex, however, and do not necessarily rule out an important “wanting” role for dopamine in positive reward (see pp. 348–349 in Berridge & Robinson, 1998, for discussion of dopamine’s shared role in positive and negative motivation).

Regardless of the role of dopamine in reward, accumbens neurons with receptors for *opioid* neurotransmitters do appear to mediate hedonic affect or “liking” as well as “wanting” for a drug or sugar reward. Rats will work to obtain microinjections of amphetamine, PCP (angel dust), and many other drugs directly into their nucleus accumbens (Carlezon & Wise, 1996). Microinjections in the nucleus accumbens of drugs that block opioid receptors can reduce the reward value of heroin or cocaine to rats, and microinjections that activate opioid receptors conversely enhance the reward value of such drugs (Stewart & Vezina, 1988). Further, activation of opioid receptors, unlike activation of dopamine receptors, does enhance the hedonic impact of sweet rewards, as measured by behavioral affective reactions elicited by the taste of sucrose (Berridge, 1996; Berridge, 2000; Peciña & Berridge, 1995; Peciña & Berridge, 2000; Rideout & Parker, 1996; Treit & Berridge, 1990).

It has recently become clear that one subregion of the nucleus accumbens in particular (an outer wrapping called the “shell”) contains opioid receptors that can cause increases in the capacity of tasty food rewards to trigger “liking” or hedonic impact. Susana Peciña and I have found that microinjection of morphine, which activates opioid receptors, directly into a posterior and medial region of accumbens shell is sufficient to increase the ability of a sweet taste to elicit positive affective reactions (Peciña, 1998; Peciña & Berridge, 2000). Thus accumbens neurons that have opioid receptors seem to be a true hedonic substrate capable of enhancing a natural sensory pleasure.

Lateral Hypothalamus

The hypothalamus was perhaps the first brain structure to be highlighted by functional affective neuroscience nearly a half-century ago. A host of discoveries in the 1950s and 1960s on the behavioral consequences of lesions and stimulation cemented the status of the hypothalamus as crucial to motivations such as sex or hunger, and to emotional displays (Stellar, 1954; Teitelbaum & Epstein, 1962). Lesions of the lateral hypothalamus in rats or cats abolish eating, drinking, sexual behavior, and several other forms of motivated behavior. Conversely, eating and social or defensive aggression are increased by lesions to the ventromedial hypothalamus.

When the firing patterns of lateral hypothalamic neurons in rats, rabbits, or monkeys have been studied by electrophysiological recording, neurons have been found that fire to the hedonic properties of food rewards, and even to the mere sight of food (Rolls, 1999; Schwartzbaum, 1988). Rolls and colleagues found that lateral hypothalamic neurons in monkeys responded to the reward properties of food, in that they fired more when the monkey was hungry than after it had eaten to satiation (Rolls, 1999; Rolls, Murzi, Yaxley, Thorpe, & Simpson, 1986). This sensitivity to hunger/satiety mirrors the increase in subjective or behavioral hedonic reactions to the taste of food, which occur in humans and animals when they are hungry (Berridge, 1991; Cabanac, 1992; Cabanac & Lafrance, 1990). Increases in hedonic palatability during hunger have been called alliesthesia by Cabanac (1979). The only other brain regions in monkeys known to show an electrophysiological alliesthesia response during hunger/satiation shifts are neurons in the orbitofrontal cortex (Rolls, 1999, 2000) and, to some degree, the amygdala (Yan & Scott, 1996).

Together with the discovery that electrical brain stimulation of the hypothalamus in animals could elicit motivated or emotional behavior (e.g., eating, maternal behavior towards infants, predatory attack, fearful freezing or defensive attack, hoarding behavior directed to food or other objects), the hypothalamus was firmly established as a prime substrate for the generation of motivation (Teitelbaum & Stricker, 1994). Originally, these behaviors were viewed as reflecting activation of neural circuits dedicated to hunger, sex, fear, and so on. However, a series of experiments by Valenstein and his colleagues around 1970 showed that the motivational state aroused by hypothalamic stimulation was actually quite flexible in nature and that its expression depended intimately on the predisposition of the individual and on past experience (Valenstein, 1971; Valenstein, Cox, & Kakolewski, 1969, 1970).

A further affective tone was added to hypothalamic electrical stimulation by the important discovery by Olds and Milner in 1954 of brain stimulation reward: rats would quickly learn to work in order to gain stimulation of the lateral hypothalamus or adjacent regions (Olds &

Milner, 1954). Brain stimulation reward has proved tremendously useful for identifying properties of neural circuits for reward (Gallistel, 1986; Shizgal, 1997, 1999; Yeomans, 1995). Humans, too, if they have electrodes implanted in their brains and given a button to activate them, will stimulate equivalent brain regions, sometimes thousands of times in a single session (Heath, 1972). However, whether electrical stimulation of the hypothalamus produces actual sensations of pleasure is open to doubt. For example, stimulation of the lateral hypothalamus in rats fails to enhance the ability of a sweet taste to elicit positive affective reactions (Berridge & Valenstein, 1991), even though lateral hypothalamic stimulation had earlier been suggested to increase the perceived palatability of foods because it typically causes rats to seek out and eat food (e.g., Hoebel, 1988). This discrepancy between pleasure and motivation induced by lateral hypothalamic stimulation may indicate that electrical stimulation actually evokes a more subtle psychological component of reward and incentive motivation than is captured by notions of sensory pleasure. For instance, stimulation might activate the psychological process of incentive salience or reward “wanting,” perhaps by modulating mesolimbic dopamine systems, rather than hedonic pleasure or reward “liking.” Although activation of these two processes might produce many similar consequences, they would still be different in important ways (Berridge, 1996; Berridge & Valenstein, 1991).

Ventral Pallidum

Less famous than the hypothalamus, the ventral pallidum is at least as important to *affective* reactions and is responsible for some of the effects often attributed to hypothalamic manipulations. The ventral pallidum region borders the lateral hypothalamus at its front and lateral sides. The ventral pallidum is also sometimes called the *substantia innominata*, or unnamed substance, although this label has been criticized (Heimer, Harlan, Alheid, Garcia, & de Olmos, 1997). In recent years interest in the ventral pallidum has risen as it has been recognized as part of the forebrain configuration known as the extended amygdala (connecting the amygdala, nucleus accumbens, ventral pallidum, and other structures; Heimer et al., 1997).

The sight and taste of food activates neuronal firing in the ventral pallidum as in the lateral hypothalamus (Rolls, 1999). But more than this, the ventral pallidum is uniquely necessary (among forebrain structures) for tasty foods to cause normal positive affective reactions. Destruction of ventral pallidal neurons by excitotoxin lesions abolishes hedonic reactions and causes aversive reactions (e.g., gaping and headshakes) to be elicited even by normally palatable foods (Cromwell & Berridge, 1993). Lesions of the lateral hypothalamus, by contrast, do not cause aversion to food as long as ventral pallidal neurons

remain intact (Berridge, 1996). The ventral pallidum has the unique status of being the only spot in the brain where a discrete lesion can abolish the capacity of sweet food rewards to elicit any positive affective reactions from rats (for weeks to months). Instead, after ventral pallidal damage food elicits only negative or aversive affective reactions that are normally elicited by bitter tastes (Cromwell & Berridge, 1993), suggesting the ventral pallidal neurons are crucial to the normal positive affect of sweet tastes. Electrophysiological studies of animals have implicated the ventral pallidum in other types of reward too, such as cocaine reward (Gong, Neill, & Justice, 1997; McBride, Murphy, & Ikemoto, 1999) or brain stimulation reward (Johnson & Stellar, 1994; Panagis et al., 1997).

Less is known regarding the role of ventral pallidum in positive affect for humans, as the structure is too small to study in brain imaging studies and has not received much attention in clinical patient studies. However, there are a few intriguing observations that do suggest a role for ventral pallidum in human mood and positive affect. For example, electrical stimulation of the *globus pallidus* is sometimes used in treating symptoms of Parkinson’s disease in human patients, and such electrodes might also stimulate neurons in the adjacent ventral pallidum. Electrical stimulation of the *globus pallidus* by a surgically implanted electrode contiguous to the ventral pallidum has been reported to sometimes induce bouts of affective mania that can last for days (Miyawaki, Perlmutter, Trotter, Videen, & Koller, 2000). Also, the induction of a state of sexual or competitive arousal in normal men was found to be accompanied by increased blood flow in the ventral *globus pallidus* in the same PET study that found increased blood flow in the cingulate cortex (Rauch et al., 1999).

Thus, ventral pallidal neurons may play a special role in affective processing, especially in generating positive affective states. In animals, activity in the ventral pallidum plays a unique causal role in generating the core process of food pleasure, enabling the normal hedonic reaction to “liked” food rewards. In humans, ventral pallidal activation may be correlated with a number of types of positive affective states.

Septum

The septum is known in animal affective neuroscience chiefly for the syndrome that results when it is damaged. In rats, “septal rage” is a consequence of septal lesions. Though ordinarily timid toward humans, after septal lesions rats have been reported to leap from their cages to attack their handlers and to persistently attack other rodents. The phenomenon, however, may not reflect release of pure aggression so much as a kind of heightened “defensive irritability.” Animals from other species (mice, monkeys, etc.) do not show increased propensities to at-

tack after septal lesions, but rather increases in the tendency to avoid or flee social partners, or other increased aspects of emotionality (Albert, Walsh, & Jonik, 1993).

In humans, the septum has been linked to *positive* affect evoked by brain stimulation by a few early reports primarily by Heath (1972). He emphasized positive mood shifts and pleasure evoked in schizophrenic and other patients, who had had electrodes or injection cannulae implanted in their brains, when electrical or pharmacological stimulation was delivered near the lateral septal nuclei (Heath, 1972). The septal location chosen by Heath may have been influenced by the fact that the title of the original 1954 report of brain stimulation reward by Olds and Milner emphasized “electrical stimulation of the septal area” in rats. However, it later became clear that Olds and Milner’s brain stimulation reward effect was chiefly due to the lateral hypothalamus and associated pathways. It is likely also that the human stimulation similarly activated front and upper regions of the lateral hypothalamus and ventral pallidum, as well as the posterior region of the nucleus accumbens, and the fiber bundles that connect these regions, as much as septal structures. Heath emphasized the pleasure reported by his subjects, which often was sexual in nature, and sometimes orgasmic in intensity. But other investigators who studied brain stimulation in humans almost never reported producing similar reports of physical pleasure in their patients (Sem-Jacobsen, 1976), and even Heath reported only a few patients with intense affective reactions. In these patients, the most common and earliest effect was elevation of mood and interest and attraction to events and people. Whether the attraction was necessarily sexual is unclear, as Heath often seemed to take steps that would encourage channeling into sexual modes (providing pornographic films, etc.). As mentioned above, careful studies of brain stimulation in animals made clear that the motivation evoked was often much more flexible and subtle in nature than it appeared, and could be channeled by situational determinants (Valenstein, 1976; Valenstein et al., 1970). It is probably safe to conclude that intense pleasure produced by brain stimulation in humans is an exceedingly rare event and that its neuroanatomical basis remains unknown. Any pleasure produced by septal stimulation may actually be due to effect on neurons in other brain structures, and the relevant neural substrate for sensory pleasure has simply not yet been clearly identified for this general region of the brain.

Brain Stem Sites

Conjunction of the words “affective” and “brain stem” might seem contradictory to those who hold a dogmatic view of the lower brain as merely reflexive. But it is worth keeping in mind that almost every feeling of physical pleasure or pain felt by your forebrain must climb its way there through the brain stem. Much can happen to as-

ending signals on the way, and there is compelling reason to believe that brain stem sites themselves make important contributions to affective experience.

Pain is clearly modulated in important ways by brain stem structures, notably by the periaqueductal gray and associated projections (Budai & Fields, 1998; Hosobuchi, 1987; Young, Bach, Van Norman, & Yaksh, 1993). An active form of analgesia is generated by the periaqueductal gray system, which sends descending influences to inhibit spinal processing of pain signals, prior to their ascent (Crofford & Casey, 1999; Willis & Westlund, 1997). The activation of this brain stem analgesia system is in turn controlled intimately by larger neural networks extending to the forebrain (King et al., 1999; Liebeskind, Sherman, & Cannon, 1982; Terman, Shavit, Lewis, Cannon, & Liebeskind, 1984).

Pleasures owe part of their hedonic impact to brain stem processing too, just as pains do. The hedonic palatability of the taste of food, for example, is enhanced in rats by brain stem administration of benzodiazepine drugs (Berridge & Pecina, 1995; Pecina & Berridge, 1996). These drugs cause indirect stimulation of receptors on neurons that use gamma-amino-butyric acid (GABA) as their neurotransmitter, via activation of a benzodiazepine receptor, which is coupled to the GABA_A receptor. Benzodiazepine drugs are mostly used for their tranquilizing effects (probably at forebrain sites), but also act on the brain stem to enhance appetite and perceived palatability of foods. In humans, administration of benzodiazepine drugs can quickly lead to an increase by up to 25% in the amount of food consumed during a meal (Evans, Foltin, & Fischman, 1999). In rats, the same phenomenon of increased food intake has long been known to occur (Cooper, 1980; Wise & Dawson, 1974), and is known also to be accompanied by an increase in the positive behavioral affective reactions indicative of hedonic impact, which are normally elicited by palatable food (Berridge & Pecina, 1995; Berridge & Treit, 1986; Gray & Cooper, 1995; Parker, 1995). Microinjections of benzodiazepines are more effective at increasing positive hedonic reactions to food and eating if they are delivered to the brainstem than if delivered to the forebrain (Pecina & Berridge, 1996). The crucial brain stem site for taste pleasure enhancement appears to involve the parabrachial nucleus in the pons. Microinjection of midazolam (a benzodiazepine drug) directly into the parabrachial nucleus causes an increase in the behavioral positive affective reaction that is elicited from rats by a sweet taste (Söderpalm & Berridge, 2000), and microinjections also increase eating behavior more when delivered in the parabrachial nucleus than in other brainstem sites (Higgs & Cooper, 1996; Söderpalm & Berridge, 2000). Benzodiazepine stimulation of the parabrachial nucleus in the pons thus appears to magnify the hedonic impact of food, leading to an increase in motivation to eat. That is consistent with other evidence regarding a role for the parabrachial

nucleus in mediating learned taste aversions that change the hedonic value of food (Grigson, Reilly, Shimura, & Norgren, 1998; Spector, 1995).

Other rewards also depend on brain stem sites. For example, the pedunclopontine nucleus, another nucleus of the pons, is important to brain stimulation reward and drug reward. Lesions of the pedunclopontine nucleus disrupt the ability of drugs like morphine or amphetamine to produce conditioned place preferences in rats, even when the drugs are given systemically and reach the entire brain (Bechara & van der Kooy, 1989). Interference with neuronal transmission in the pedunclopontine nucleus also disrupts the reward value to rats of electrical brain stimulation, even when the stimulation is delivered to the lateral hypothalamus, well above the pons (Waraczynski & Shizgal, 1995; Yeomans, Mathur, & Tampakeras, 1993), although not every study has found large disruption (Waraczynski & Perkins, 1998).

The idea that the brain stem may be important in mediating human emotions in general has been recently emphasized by Panksepp and by Damasio (Damasio, 1999; Panksepp, 1998). Panksepp argues for a brain stem role based on a concept of emotional primitives (Panksepp, 1998). He suggests that the capacity for emotional reactions is so fundamental a psychological feature that it must have appeared very early in vertebrate evolution when brain organization was dominated by the brain stem (Panksepp, 1998). Panksepp argues that basic emotional states must have been originally encoded by neural systems in the hindbrain and midbrain, and that the emotional organization of human and other modern mammalian brains remains rooted today to a large degree in brain stem neural systems. In particular, Panksepp suggests that opioid neurotransmitter receptors in the periaqueductal gray area of the midbrain are important to many emotional states, on the grounds that drugs that act on opioid receptors have been shown to alter many different types of motivation and emotion (pleasure, pain, hunger, sex, maternal behavior, etc), and the periaqueductal gray is site of a major opioid system that might influence those emotional states.

Damasio has arrived at a related conclusion about the importance of brain stem systems to human emotion and self-awareness (Damasio, 1999). His argument is based on the clinical neurological observation regarding human patients that the type of brain damage that most often causes an utter loss of all consciousness, and production of a deep coma or vegetative state, typically involves the brain stem, especially the area of the midbrain in front of the trigeminal cranial nerve (Damasio, 1999). This pretrigeminal area of the brain stem, Damasio argues, works in conjunction with forebrain structures, such as the cingulate cortex and prefrontal cortex, and is fundamentally important to the generation of consciously aware states of all types, including emotional states. Thus evidence from

both humans and animals suggests the brain stem may be rather more important to pleasure and pain than has commonly been presumed.

Left and Right: Hemisphere Specialization

Distinct from the question of the role played by particular brain structures or levels in affect and emotion is the question of whether structures on the left side of the brain make a contribution different from those on the right side. The lateralization question is important for understanding the organization of affect in the brain, however, and so it is interesting to compare it in humans and other animals. The issue of lateralization of affective function has arisen mostly but not exclusively from studies of humans and primates (Davidson, 1992). There appear to be two types of views regarding human hemispheric asymmetry and emotion (Habib, 1998). The original view arose from "split-brain" patient studies, and suggests that affective processes in general are largely mediated by the right hemisphere (Cacioppo & Gardner, 1999). It is part of the larger and well-known hypothesis of cognitive lateralization, which suggests that the left hemisphere is best at linguistic and analytic tasks, whereas the right hemisphere may be best at recognizing and expressing emotion, as well as at spatial and holistic tasks. However, recent split-brain patient evidence indicates that the left hemisphere may not have emotional deficits per se, as the left and right hemisphere may be equally able to identify emotional facial expression in such patients (Stone, Nisenson, Eliassen, & Gazzaniga, 1996).

A quite different lateralization theory of affect has been championed especially by Davidson, who suggests that the left hemisphere predominately mediates positive affect whereas the right hemisphere mediates negative affect (Davidson, 1992, 1998b). This hypothesis has its roots in early observations that catastrophic levels of depression were produced more often in neurological patients after damage to the left hemisphere than after damage to the right hemisphere (Gainotti, 1972; Goldstein, 1952), but the idea that positive and negative affect might be segregated among cortical hemispheres was not truly developed until the 1980s, when a number of studies began to provide converging evidence (for reviews see Davidson, 1992, 1998a). For example, normal human subjects may be more likely to recognize happy expressions when presented to their left hemisphere (Davidson, Mednick, Moss, Saron, & Schaffer, 1987). The left hemisphere may be more activated by EEG measures in human infants who experience a pleasant sweet taste (Fox & Davidson, 1986) or adults who view photographs of a positive emotional scene (Lane et al., 1997), or report positive emotional self-evaluations (Sutton & Davidson, 1997).

In support of the hypothesis that negative affect is a right-hemisphere specialization, recognition of fear

expression has been reported to be most impaired after right-hemisphere damage (Adolphs, Damasio, Tranel, & Damasio, 1996). The right hemisphere may be more activated by EEG measures in human infants who are distressed (Davidson & Fox, 1989), or by PET or fMRI measures in adults who receive an unpleasantly salty taste (Zald et al., 1998), a repeated painful stimulus (Hsieh et al., 1999), or photographs of negative emotional scenes (Canli, Desmond, Zhao, Glover, & Gabrieli, 1998). Similarly, the right hemisphere is more activated in depressed adults who report sadness (Davidson et al., 1999; Mayberg et al., 1999).

The selective impairment of positive affect by left cortical damage, or impairment of fear by right cortical damage, seems often to be interpreted in terms of release of the *opposite hemisphere's* affective function. An alternative to that view is that the emotional change actually reflects release of *subcortical structures* below the damaged cortex but on its own side (Tucker, 1981; Tucker et al., 1995). By this alternative "within-hemisphere" interpretation, subcortical structures may have an emotional bias that is opposite to the bias of their cortex on the same side. Imaging studies of normal humans will typically reflect the cortical bias on one side (discussed below), whereas cortical damage by this view would release the opposite affective state mediated by subcortical structures on the damaged side. As yet, there is little basis on which to choose among these interesting alternative explanations.

There is some evidence from animals to support the hypothesis that manipulations of right neocortex, especially prefrontal and cingulate cortex, may alter emotional reactions, especially negative emotional reactions (Denenberg, 1983). For example, excitotoxin lesions of the right prefrontal cortex of rats, more than left prefrontal cortex, reduce the magnitude of stress hormone responses (cortisol) evoked by physical restraint stressors, as well as the consequence of gastric ulcers that can follow (Sullivan & Gratton, 1999). Unilateral destruction of dopamine projections in the right prefrontal and cingulate regions of neocortex produces an increase in stress-induced gastric ulcers to a greater degree than unilateral destruction on the left side of the brain (Sullivan & Szechtman, 1995). The reason right prefrontal excitotoxin lesions *decrease* responses to stress whereas right dopamine-depleting lesions *increase* them may be that excitotoxin lesions destroy the cortical neurons themselves, whereas dopamine depletion leaves the cortical neurons intact and merely removes dopamine axons to them that might normally exert inhibitory effects. Whether right neocortical dominance for emotional responsiveness is specific in rats to responses with negative emotional valence is not yet entirely clear. The right hemisphere might also be important in reward, as more dopamine release has been suggested to occur in right prefrontal cortex than left prefrontal cortex of rats learning to press a bar to gain drug reward in

the form of an intravenous morphine infusion (Glick et al., 1992).

Finally, some evidence also suggests a lateralization of function regarding reward mediated by *subcortical* brain systems at least in rats. This lateralization may not be consistently localized to the left or right side in particular, but instead localized to the same side of a rat's brain that is dominant for motor function (Glick, Weaver, & Meibach, 1980, 1981). Individual rats have one side of the brain specialized for motor dominance, as do individual humans, but the dominant side is distributed nearly equally between left and right hemispheres across the rat population (unlike humans, who most commonly are right-handed and left motor-dominant). The association of subcortical reward-dominance with motor-dominance has been suggested to reflect the involvement of both functions with mesolimbic/nigrostriatal dopamine projections (Glick et al., 1980, 1981).

A few other studies have also been interpreted as reflecting emotional lateralization in nonhuman animals (Davidson & Sutton, 1995). In Old World monkeys, Davidson and colleagues found that a shift from right to left EEG dominance was produced together with a reduction of fearful freezing after administration of a diazepam tranquilizer (Davidson, Kalin, & Shelton, 1993). In an interesting study of lateralized facial expression by New World monkeys, Hook-Costigan and colleagues reported that larger movements were made on the side of the mouth controlled by the left brain hemisphere (right side of the mouth) when they made emotionally positive vocalizations (social contact calls), but larger movements were made on the side of the mouth controlled by the right brain hemisphere (left side of the mouth) during emotionally negative facial expressions (fear; Hook-Costigan & Rogers, 1998). These results are consistent with the hypothesis that the right brain mediates negative affect, whereas the left brain mediates positive affect, and thus emotional lateralization may extend at least in primates. Finally, one study suggested that anxiety in rats may be increased by stimulation of the right amygdala but not of the left amygdala (Adamec & Morgan, 1994), suggesting a possible subcortical right bias for negative affect even in rats. The degree to which brain systems of affect are lateralized more generally in animals deserves to be explored further.

Comparing Humans and Other Animals

Human and Animal Similarities From This Review

A major point to be taken from this survey of brain systems in affective impact is that there is no qualitative difference between humans and other animals. Each brain

structure surveyed here, from prefrontal cortex to brain stem, is similarly implicated in humans and other animals, whenever the evidence allows direct comparison. There is no substantial disagreement between the results of human imaging or clinical patient studies, on the one hand, and, on the other, animal electrophysiological recording, neurochemical measurement, brain stimulation, brain lesion, or pharmacological manipulation studies.

For both humans and other animals, brain mechanisms of affective reaction are distributed widely throughout the brain. Even in humans, the brain stem plays a potent role in modulating affective reactions. For example, the affective component of human pain is certainly modulated by opioid activity in the periaqueductal gray and associated regions (Budai & Fields, 1998; Hosobuchi, 1987; Young et al., 1993). Human appetite and the positive hedonic component of food palatability may also be modulated in part by benzodiazepine receptors in human brain stem, though crucial evidence from humans remains to be collected.

Conversely, even in rats, the prefrontal cortex plays a role in emotional responses. Lesions of prefrontal cortex disrupt delayed foraging for rewards (Seamans et al., 1995), and microinjections into prefrontal cortex are rewarding. Thus from prefrontal cortex to brain stem, each brain structure reviewed here can be seen to play a comparable role in all mammals, from humans to rats.

Differences Between Human and Animal Affective Neuroscience

Yet there is an enormous gap between humans and other animals in the *relative weight* given to conclusions about the role of cortical regions and subcortical brain structures in the affective neuroscience literature, even if the difference is not all or none. The overwhelming majority of statements that *prefrontal or cingulate cortex* are important substrates for emotion comes from studies of humans, or at least, of primates. Investigators who study humans or primates are the authors of all theoretical formulations of brain and emotion that emphasize cortical areas (Damasio, 1994; Davidson et al., 1999; Rolls, 1999). It is no accident, by contrast, that authors who stress the importance of *subcortical brain structures* in affective reaction have been investigators whose research has primarily been on brain mechanisms of emotion and motivation in rats (Berridge, 1999; Davis & Lee, 1998; Gray, 1987; LeDoux, 1996; Panksepp, 1998; Toates, 1994).

In part, *artifactual differences* in technique and conceptual approaches may account for the discrepant emphases on “human cortical emotion” versus “animal subcortical emotion.” The questions and methods used to approach brain substrates of feeling and emotion are quite different in studies of humans from studies of animals. This is partly why different brain structures have been highlighted in different species.

Human brain imaging studies of emotion are biased to concentrate on cortical brain regions rather than subcortical regions for several reasons: (1) human studies use *cognitive* tasks to evaluate emotion, which are more likely to recruit cortical regions; (2) the functional architecture of cortical modules is better suited to register on regional activation scans than is subcortical architecture; (3) *correlational* measures of emotion like functional brain imaging will include cortical regions that are activated during an emotion even if those regions may be incapable of causing the emotion, or may not actually be needed for the emotion; and (4) human patients with brain damage used in studies of emotion are more likely to present with lesions in cortical than subcortical sites. Conversely, animal studies of emotion are biased to focus on subcortical structures because (1) tests of emotion in animals involve relatively little abstract cognitive evaluation, and instead focus on a behavioral or physiological reaction to a strong innate or conditioned emotion-arousing stimulus; (2) *causation* of a particular emotional reaction by a brain event seems more likely to result from manipulation of subcortical regions than of cortical regions; (3) subcortical structures seem more likely than cortical regions to prove absolutely *necessary* to the induction of a particular emotional reaction.

Emotional Cognition Versus Basic Emotional Reaction

Human brain imaging studies of emotion could be said typically to focus on *emotional cognition* (as opposed to cognition that is emotionally or affectively more neutral, which is the focus of other cognitive neuroscience studies). Such tasks often involve high-level cognitive evaluation of emotional meanings of language stories or of complex pictures, or cognitive induction of an emotional state through these cognitive symbols. Normal individuals or brain damaged patients are usually asked to judge the emotional *significance* of a face, voice, scene, or word. Can they recognize fearful from friendly or cheerful from sad? Such stimuli require complex perceptual and symbolic decoding, at least, and often further thematic and cultural decoding. Human studies of adult emotion are inevitably highly cognitive in this sense (Ellsworth, 1994a; Ellsworth & Scherer, this volume; Kitayama & Markus, 1994). A cognitive approach to emotion is most likely to highlight cortical involvement. It is interesting to note that in the rare psychological theory of human emotion in which affect is conceived as *separate* from cognition, such as that of Zajonc and colleagues (Zajonc, 1980, 1998), the most often referenced brain substrates for emotional reaction are the amygdala and its subcortical connections.

Animal studies of emotion, by contrast to most studies of humans, often aim to produce strong *emotional states* directly, either by presentation of a primary affective stim-

ulus for fear, hunger, or the pleasure of sex or food, or by the brain manipulation itself. One does not measure the animal's emotional judgment or categorization but rather its behavioral or physiological *emotional reaction*. The question asked is not what motivational *meaning* a stimulus has but rather what emotional or motivational *state or reaction* has been produced or modulated by an event or brain manipulation.

Affective neuroscience studies of monkeys performing discriminative reward tasks may be exceptions to the rule that animal studies are always about emotional reaction rather than emotional cognition (Rolls, 1999; Schultz, 1998). Electrophysiological studies often ask the monkeys to recognize the emotional meaning of a stimulus, acquired by associative learning or by a cognitive rule. This may be one reason studies of monkeys have highlighted neocortical regions for mediating emotion to a greater degree than studies of other animals. The greater cognitive sophistication of monkeys allows use of tasks that rely on stimulus meaning rather than immediate emotional state. Behavioral neuroscientists are generally hesitant to induce strong emotional states such as fear or hunger in monkeys, partly for ethical reasons and partly because these investigators typically use the same monkeys in several consecutive experiments. A strong emotional manipulation in one experiment might alter results in subsequent experiments, and hence is avoided by investigators. For these reasons, the procedures from affective neuroscience studies of monkeys have tended to be as cognitive as possible, and so may have maximized the role of cortical areas.

Brain Correlation Versus Causation of Emotion

Another artifactual source of the discrepancy between human and animal affective neuroscience comes from the fact that most current studies of humans tend to focus on brain activation that is *correlated* to emotion whereas studies of animals focus to a greater extent on manipulations that *cause* observable changes in emotional reactions. Both correlational and causal evidence indicate that a brain structure mediates emotion, but the word "mediates" has more than one meaning regarding brain-behavior relations (Sarter, Berntson, & Cacioppo, 1996).

To mediate can mean that activation of the brain structure is a reliable correlate to the emotion, independent of whether it causes the emotion. This is the case when studies of brain activation identify particular neural substrates as especially activated during an emotion. Mediate can mean alternatively that activation of the brain structure is causally *necessary* in order for the emotion to occur, and that the emotion never occurs in the absence of the structure, as when a lesion disrupts affective reaction. Mediate can also mean that activation of the brain structure is causally *sufficient* (all else being equal) to trigger the emotion. Or mediate can mean any combination of these. It can

mean even more complex and subtle mind-brain relations, such as those involved in distributed neural processing, or the dynamic capacity of neural systems for reorganization after damage (Farah, 1994; Sarter et al., 1996; Winkelman, Berntson, & Cacioppo, 2001). We often say that a brain structure mediates a particular psychological function, as though the term "mediate" had one clear meaning, which combined all of these senses equally: brain activation correlated to a function, necessary for the function, and sufficient to cause the function (all else being equal). But we make a mistake when we do so without recognizing the difference among these claims.

It can perhaps be stated as a general axiom that correlational studies, which measure neural activation correlated to a psychological function (PET, fMRI, EEG, electrophysiology, Fos, etc.), will always implicate a greater number of brain regions than causal studies, which measure changes in the function caused by brain manipulations (lesions, stimulation, drug microinjection, etc.). There are more correlates than causes. This is because the two approaches rely on entirely different senses of mediation. The two approaches mean different things when they say "brain area X mediates psychological function Y."

Brain Imaging Biases for Cortical Spatial Segregation

Human brain imaging techniques such PET or fMRI have a special measurement-related feature that biases them toward neocortex, irrespective of the importance of subcortical structures (Sarter et al., 1996). PET and fMRI techniques are designed to detect changes in regional *blood flow*. These measures exploit the remarkable ability of the brain's vascular system to change blood delivery to cerebral blood vessels, based on the changing needs of active neurons, which increase their uptake of glucose and oxygen when they fire. They detect a change within one spatial region and compare it to other regions. The crucial word here is "region": the blood flow measure requires that the psychological functions of interest be parceled out to widely separated parts of the brain.

For this imaging technique to implicate a particular brain region in emotion, the neurons devoted to the emotional state must (1) be grouped together densely in one area and (2) separated from neurons devoted to other functions. Only then can an increase in the combined neuronal metabolic uptake be sufficient to trigger a vascular response. No signal would be detected if the neurons mediating a function either were distributed widely across the brain. Likewise, no signal would be detected if the neurons for one function were densely packed close together with neurons mediating functions activated by other tasks.

The neocortex is most likely to register on fMRI and PET imaging techniques partly because of its sheer size in

human beings and partly because the neocortex segregates functions especially well across spatial regions. By contrast, even if the brain stem or hypothalamus had segregation of psychological functions across different neurons to an equal degree as in the cortex, the “labeled line” code of those dedicated neurons are less likely to appear on an fMRI or PET scans. The neurons in those structures are too closely packed together to allow subpopulations to impact on vascular blood flow. In upshot, human imaging studies of psychological function are biased to detect functional correlations to neocortical regions rather than to subcortical brain structures.

Cortical Biases in Studies of Human Patients

To a lesser extent, studies of human patients with brain damage are also inherently better suited to specify contributions of neocortex than to reveal the role of subcortical structures (other than the amygdala, which is isolated in neocortex). First, lesions of neocortex are more likely to be localized to a *single region* than are subcortical lesions. Cortical lesions are more likely to produce a *single functional consequence*, rather than a host of many consequences. The neocortex is sufficiently large that a lesion in one cortical lobe may leave most other cortical lobes untouched, as well as most subcortical structures. Further, the neocortex is especially vulnerable to external injury. Wounds or other injury may sometimes destroy a cortical region without damaging deeper brain structures. Even some forms of brain disease tend to damage neocortex most, and these are the most prominent diseases in the clinical neuropsychological literature. For example, epilepsy, with its predilection for temporal lobe foci, often causes specific bilateral temporal lobe and amygdala damage. That allows analysis of the psychological functions of those structures, with a specificity of pathology that cannot be matched for most other brain structures.

Subcortical lesions, if they are large enough to cause bilateral damage to a particular subcortical structure, are more likely to destroy neighboring subcortical structures in addition. Parkinson’s disease and medial hypothalamic tumors are two exceptions to this rule, as they can cause bilateral damage specifically in the nigrostriatal system or in the ventromedial hypothalamus. But, in most cases, subcortical lesions that are large enough to be interesting damage more than one subcortical structure. Subcortical brain lesions are also more likely to produce generalized or even catastrophic functional deficits, such as coma. Naturally such broad deficits tend to preclude psychological analyses.

For these reasons, studies of human patients after brain damage, just as studies of human brain imaging, have been better at providing information about the roles of cortical areas than about subcortical brain structures. Conclusions from such studies naturally are biased to emphasize the

role of neocortex. Since these studies are conducted invariably in humans, it has produced an impression that human brain organization of emotion is disproportionately weighted toward the amygdala and neocortex.

Encephalization Differences Between Human and Animal Emotional Brains

I have stressed the degree to which perceived animal/human differences in the brain’s organization of feeling and emotion are probably due to artifacts rather than to a real gap between primates (including humans) and other mammalian orders. But that is not to say there is no real difference at all between humans and other animals. There may indeed be a real difference in brain organization of emotion. If so, however, it is quantitative in nature and moderate in degree—not a qualitative or massive difference.

The chief evidence for a difference is that emotional processes may be somewhat more susceptible to disruption by cortical damage in humans than in other animals. Humans can be devastated, rendered into vegetative states, by large neocortical lesions, whereas a rat can lose its entire neocortex and continue on remarkably normal (Panksepp, Normansell, Cox, & Siviy, 1994; Skinner et al., 1994; Whishaw, Schallert, & Kolb, 1981; Wirsig & Grill, 1982). To some extent this may reflect the increased influence of cognition on emotional processes in humans and primates to which we have already alluded. But alternatively it may also reflect a subtle primate reorganization of the neural bases for emotional core processes themselves. This difference may be captured by the term “encephalization” from the study of brain evolution.

Encephalization describes the physical expansion in evolution of human neocortex and forebrain structures compared to other animals (Jerison, 1977). It applies to primates in general, but especially to humans. Human neocortex is large compared to neocortex in other mammals. The only other mammals to own comparably large neocortices belong to the order of cetaceans, comprising dolphins and whales (Marino, 1998). But the internal microstructure of neocortex in cetaceans appears to be much simpler and primitive compared to primate neocortex (even compared to most other nonprimate land mammals; Morgane, Jacobs, & Galaburda, 1985). Thus primates probably have an uncontested lead in their net complexity of cortical computation. Humans are paramount in terms of *functional encephalization*, the relative degree of neural information processing given over to neocortex.

What is the psychological consequence of human functional encephalization? In one sense this question seems easy to answer: only humans read books about emotion. Human cognition is our distinguishing feature, and cognition exerts myriad influences over the human experience of emotion. Human emotional life is psychologically

richer compared to that of other animals: it is laden with symbolism and culture, linguistically elaborated to ourselves and to each other (Cacioppo & Gardner, 1999; Ellsworth, 1994a; 1994b; Ellsworth & Scherer, in press; Kitayama & Markus, 1994; Nisbett & Wilson, 1978; Wilson, Hodges, & LaFleur, 1995; Winkielman et al., 2001; Zajonc, 1998). No doubt human neocortex plays a vital role in the cognitive elaboration of this psychological richness of human emotion. In this sense, cognition may feed back upon, and perhaps change, human emotional core processes.

Emotional Re-Representation in Neocortex

But there may also have been a change in the neural organization of emotional core processes. Emotion has not “moved” in humans to the neocortex from subcortical structures, in this sense, but its center of gravity may have shifted slightly upward. Our understanding of functional encephalization owes a lot to the early insights and writings of John Hughlings Jackson, a 19th-century British neurologist. Hughlings Jackson surmised principles for the organization of functions embodied at different levels of the brain, based on the movement deficits of his patients with damage to those levels. The lowest portions of the brain, he suggested, simply *represented* the outside world and the programs needed for movement. By themselves, low levels were capable of triggering simple responses to appropriate simple stimuli. Higher levels of the brain, in turn, rerepresented those original neural representations. Higher levels were forced to work with the products of those lower levels, since there was no other way for them to get input about what was happening. But higher levels *transformed* the lower products they received: “They represent over again in more complex, etc., combinations, the parts which all middle centres have re-represented, and thus they represent the whole organism; they are re-representative” (Hughlings Jackson, 1958, p. 42).

Re-representation captures the iterative nature of hierarchical representation as one ascends the brain. High levels do not replace the lower levels in a hierarchical brain, nor take over themselves the representative functions originally performed by those lower levels (Gallistel, 1980). The lower levels remain responsible for their original representations. Higher levels rather reproduce those lower representations as re-representations, and in doing so add new and abstract features. Cortical re-representation of emotional signals, with increasingly abstract features at upper levels, provides one way to conceive of the elaboration of human emotional processes in terms of encephalization (Gallistel, 1980; Rolls, 1999).

Finally, the encephalized re-representation of emotion in humans has implications for a change in the *autonomy* of subcortical structures. Subcortical systems in a hierarchical system do not give up their emotional functions to higher levels. But subcortical systems do give up auton-

omy—their independence—in a hierarchical system as higher, abstract representations become increasingly dominant (Gallistel, 1980). Higher units can influence lower levels, and that happens in both humans and rats. A difference between humans and rats, however, is the *magnitude* of descending inputs that impinge ordinarily upon subcortical systems. Human subcortical systems receive greater cortical inputs ordinarily. But not only that, they are wired to a greater degree to *expect* that cortical input. There is a cost to this: greater vulnerability to disruption when the expected cortical input to a subcortical system suddenly disappears. The visible manifestation of this difference is that human psychological function, even for basic psychological processes, is relatively disturbed by a cortical lesion that would have minimal impact in the brain of another mammal. This is not to say that emotion has *moved* from subcortical structures to the cortex in humans. Human core processes of emotion may remain grounded in subcortical brain structures (Berridge, 1999; LeDoux, 1996; Panksepp, 1998; Zajonc, 1998). It may be truer to say instead that feeling in humans may have “spread upwards.” The tendrils of emotional core processes extend from their original homes in subcortical structures to more fully integrate cingulate and orbitofrontal regions of the human neocortex into their subcortically based computations.

Conclusion

Neural substrates of feeling and emotion are distributed throughout the brain, from front to back, and top to bottom. The same brain structures are implicated in affective reactions for both humans and other animals. Orbitofrontal and other prefrontal cortex, cingulate cortex, amygdala, nucleus accumbens, ventral pallidum, mesolimbic dopamine and opioid systems, hypothalamus, midbrain, and brain stem sites—all play a role in affective reaction, whether of a human, monkey, or rat. The divergence in relative emphasis placed on neocortical regions versus subcortical structures in the literature on emotion has occurred largely because of methodological differences between human affective neuroscience and animal affective neuroscience. Human affective neuroscience has been dominated by correlational studies of neural activation, whereas animal neuroscience has given greater weight to causal studies involving brain manipulation that change emotional states and reactions.

The difference in cortical/subcortical emphasis arises also because of conceptual differences in the kind of questions asked of its subject by each subfield. Human affective neuroscience studies have tended to measure emotional cognition and judgments, whereas animal affective neuroscience has tended to measure basic affective reactions. Finally, the relative emphasis on neocortex in human

emotion may also stem in part from the greater role of cognitive evaluation in elaborating cognitive aspects of human emotion.

Human evolution has changed only one major aspect of the organization of emotional core processes within the brain—namely, the *degree of encephalization* for particular emotional functions. Encephalization has modified the autonomy of subcortical structures, so that neocortical inputs have become incorporated into subcortical function to a greater degree than in nonhuman animals, so much so that human subcortical function cannot be maintained normally when cortical inputs are suddenly removed. This encephalization has not *relocated* emotional core processes from subcortical to cortical structures, but it has *expanded* the penumbra of emotional core processing circuitry into upper layers of the brain. This is reflected in humans by pronounced cortical activation during affective reactions and by a special human vulnerability to disruption of psychological function after neocortical damage. Encephalization in humans reports an important evolutionary tweak of preexisting neural organization—a modification that transforms the capacity of the human emotional brain in fascinating ways but does not replace the basic emotional brain that we share with other animals.

NOTES

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1. I accept the admonition of Dess and Chapman that the term “animals” should not be used to exclude humans, who in the most relevant sense are animals, too (Dess & Chapman, 1998). In most cases, I will try to make clear that I mean “animals other than humans,” or sometimes “animals other than primates.” In other cases I hope the reader will accept the use of “animals” as a shorthand for those phrases.

2. Every brain structure discussed in this chapter actually exists as a paired structure, with one half on the left side of the brain and one on the right side. Thus one should say that the left and right prefrontal cortices lie at the very front of the brain. For the sake of simplicity, I will speak of each brain structure as a singular entity (and leave implied the true bilateral symmetry).

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Richard J. Davidson

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