31 The Functional Neuroanatomy of Emotion and Affective Style

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This chapter presents an overview of recent research on the functional neuroanatomy of human affective processes, focusing on studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). Where relevant, some studies on patients with discrete lesions are also included, as well as animal studies that provide much of the foundation for the modern human work. Research on patients with mood and anxiety disorders is, for the most part, not included as such studies have been extensively reviewed in a number of recent publications.[1–6] Over the past 10 years, there has been an enormous increase in animal research that has provided a detailed foundation for understanding the neural circuitry of several basic emotional processes.[7] This corpus of literature has helped to make emotion a tractable problem in the neurosciences and has led to the development of affective neuroscience.[8] With recent advances in functional brain imaging, the circuitry underlying emotion in the human brain can now be studied with unprecedented precision (see Box 31.1).

The Functional Neuroanatomy of Approach and Withdrawal-related Emotion

Two basic systems mediating different forms of motivation and emotion have been proposed.[9–12] Although the descriptors chosen by different investigators varies and the specifics of the proposed anatomical circuitry is presented in varying levels of detail, the essential characteristics of each system are similar across conceptualizations. The *approach* system facilitates appetitive behavior and generates certain types of positive affect that are approach-related, for example, enthusiasm, pride, etc.[13] This form of positive affect is usually generated in the context of moving toward a desired goal (see Refs. 14, 15 for theoretical accounts of emotion that place a premium on goal states). There appears to be a second system concerned with the neural implementation of *withdrawal*. This system facilitates the withdrawal of an individual from sources of aversive stimulation and generates certain forms of negative affect that are withdrawal-related. For example, both fear and disgust are associated with increasing the distance between the organism and a source of aversive stimulation. A variety of evidence drawn from multiple sources suggests the view that the systems that support these forms of positive and negative affect are implemented in partially separable neural circuits. The key elements of the circuitry are reviewed below.

Prefrontal Cortex

A large body of lesion, neuroimaging and electrophysiological data supports the view that the prefrontal cortex (PFC) is an important part of the circuitry that implements both positive and negative affect. There are several important subdivisions of the PFC that are critical to note with respect to affective processing. First are the distinctions among the dorsolateral, ventromedial and orbitofrontal sectors and the second is the distinction between left and right sectors within each of these regions of PFC (see Fig. 31.1).

A number of early studies that evaluated mood subsequent to brain damage suggested that patients with damage to the left hemisphere, particularly in PFC, were more likely to develop depressive symptoms compared with patients having lesions in homologous regions of the right hemisphere.[16–18] Most of the lesions in these studies are large and include more than one sector of PFC. However, dorsolateral PFC is affected in the majority of patients represented in these studies. The general finding of left dorso-

Box 31.1
Conceptual and methodological complexities in neuroimaging studies of human emotion

PET and fMRI provide powerful and complementary information that has not been possible to acquire with other methods. These techniques enable scientists to examine regional patterns of activation in normal intact humans with considerable spatial precision and, in the case of fMRI, with temporal resolution on the order of seconds. With PET, in addition to its use as a measure of hemodynamic or metabolic activity, it can also be used to probe components of neurotransmission *in vivo* in relation to behavioral performance (Ref. a). The application of these methods to the study of emotion has burgeoned over the past several years and has generated a new body of literature on the circuitry associated with selective features of emotional responding and affective traits. There are a number of critical conceptual and methodological issues that are fundamental to neuroimaging studies of emotion:

(1) The perception of emotional information must be carefully distinguished from the production of emotion. There are many studies that present as stimuli to subjects, facial expressions of emotion. The presentation of facial expressions of emotion does not necessarily (nor even likely) elicit any emotion. Thus, when investigators use this procedure it is important that it be described as a study of the perception of emotional faces and not a study about emotion *per se* (Refs b,c).

(2) The control conditions against which emotion activation is compared crucially influences the nature of the data obtained. When using subtractive methodology, it is helpful to control for as much of the stimulus content as possible to isolate the effects of emotion itself. For example, the comparison of a condition during which subjects were self-generating emotional imagery to a resting baseline would be problematic (Ref. d) because any effects observed might not be a function of the particular emotion that was aroused, but rather the cognitive processes involved in retrieving information from memory and voluntarily generating visual imagery. It is good practice to include more than one emotion condition (e.g. both positive and negative), as any effect produced as a consequence of simply generating emotion *per se* should be common to the two emotions, while differences between conditions can be attributed to the specific nature of the emotional process elicited.

(3) Stimuli designed to elicit different emotions must be matched on arousal and on physical characteristics. Arousal can be inferred in several different ways including self-report and skin conductance measures (Ref. e). Differences in patterns of activation observed between two emotion conditions that are not matched on intensity or arousal can obviously result from a failure to match appropriately and might be more a function of the arousal differences rather than the emotion differences between conditions (see Ref. f for more extended discussion). A related issue is the need to match stimuli across emotion and control conditions on physical properties, such as color, the presence of faces, spatial frequency, etc. Some differences found between emotion conditions might conceivably be a function of physical differences between the stimuli that have nothing directly to do with emotion. For example, in our fMRI studies of emotion induced with pictures, we have found (Ref. g) that activation of secondary visual cortex by negative pictures compared with neutral pictures may in part be a function of the color differences between these classes of stimuli.

(4) Putatively asymmetric effects must be rigorously statistically interrogated. Many investigators using both PET and fMRI have reported asymmetric changes associated with emotion (Ref. h). In most cases, claims about an activation being asymmetric were made on the basis of voxels in one hemisphere that exceeded statistical threshold while homologous voxels in the opposite hemisphere did not. However, such an analytic strategy, while typical, tests only for the main effects of the condition. To demonstrate an actual difference between the two hemispheres, it is necessary to test the Condition X Hemisphere or Group X Hemisphere interaction. The fact that such tests are rarely performed is largely a function of the fact that software is not

Box 31.1
(continued)

commercially available to perform such analyses for the entire brain volume. If this interaction was not significant, it is not legitimate to claim that an asymmetric finding was observed since the lack of a significant interaction means that the changes found in one hemisphere were not significantly different from those observed in the other, even if the effects were independently significant in one hemisphere but not in the other. Moreover, it is possible for significant interactions to arise in the absence of any significant main effects. As discussed in the main text, very few investigators who have reported asymmetric effects have properly tested for the Condition X Hemisphere interaction.

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lateral PFC damage increasing the likelihood of depressive symptoms has been interpreted to reflect the contribution of this cortical territory to certain features of positive affect, which, when disrupted, increases the probability of depressive symptomatology. This line of reasoning is consistent with the idea that depression is associated with deficits in positive affect.[19] Recent reviews of the modern literature on this topic[20] have largely supported these earlier studies, though some inconsistencies have been reported[21,22] (see Ref. 23 for discussion of conceptual issues in this literature). Morris et al.,[24] in a study with the largest sample size yet for research of this kind ($N = 193$) and with patients who were in the acute stage of stroke (all patients were tested between 7 and 10 days post-stroke), found that it was only among patients with small-sized lesions that the relation between left PFC damage and depressed mood was found. Larger lesions probably intrude on other cortical sectors and may obscure the relationship between left PFC damage and depression.

Bechara and colleagues have amassed considerable evidence over the past several years that patients with bilateral lesions of the ventromedial PFC cannot anticipate future positive or negative consequences of their actions, although immediately available rewards and punishments do influence their behavior.[25] Such patients also fail to show anticipatory electrodermal responses when confronted by a risky choice whereas normal controls generate such anticipatory autonomic responses even before they explicitly knew

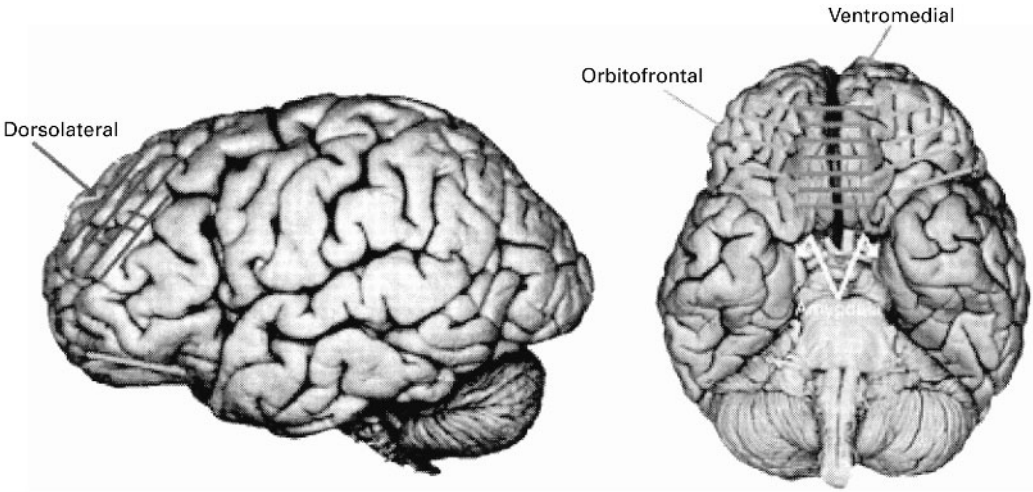

Figure 31.1
Sectors of human prefrontal cortex. (Left) Lateral view indicating dorsolateral (blue), ventromedial (red) and orbitofrontal (green) cortical territories. (Right) ventral view indicating ventromedial (red) and orbitofrontal (green) cortical territories. Also indicated are the amygdalae located on the medial margin of the temporal lobes, just dorsal to the unci which are identified by the tips of the arrowhead (yellow; see Fig. 31.2). (Adapted from Ref. 93.)

it was a risky choice.[26,27] Recently, this group[28] demonstrated a double dissociation whereby patients with anterior ventromedial PFC damage were impaired on a gambling task that assesses anticipation of future positive and negative consequences while performing normally on a working memory task (delayed non-matching to sample). Patients with right dorsolateral PFC damage were impaired on the working memory task while performing normally on the gambling task. Whether separable influences on the anticipation of positive or negative consequences would result from unilateral left- versus right-sided ventromedial damage respectively, has never been studied.

The differential involvement of the left and right PFC in certain forms of positive and negative emotion is supported by electrophysiological measures of regional activation in normal subjects exposed to stimuli that elicit emotion.[12,29–31] These studies find increased left anterior activation during positive affect and increased right-sided anterior activation during negative affect. A major limitation of these studies is the lack of spatial resolution afforded by the electrophysiological measures.

Using an extended-picture-presentation paradigm to induce consistent changes in positive or negative mood,[32] we measured regional glucose metabolism using PET while we independently and objectively verified the presence of the intended emotional states using emotion-modulated startle and facial electromyography.[33] During the production of negative affect, we found right-sided increases in metabolic rate in both inferior and superior regions of the PFC including the anterior orbital, inferior frontal, middle frontal and superior frontal gyri. During the production of positive affect, a pattern of predominantly left-sided activation was observed with a somewhat more posterior distribution compared with negative affect. During positive

affect, left-sided metabolic increases were observed in the region of the pre- and post-central gyri. In addition, increases were observed in the region of the left nucleus accumbens (discussed below).

Relatively few other neuroimaging studies have compared objectively verified positive and negative affect in the same subjects. Some studies have examined patterns of activation that were common across emotions in comparison with a neutral baseline condition.[34] In this latter study, Lane et al. reported that the emotion conditions produced significantly greater activation in the medial PFC compared with the neutral control condition. A very similar finding was obtained in an independent sample of subjects exposed to pleasant, unpleasant and neutral pictures, with the emotional pictures producing increased activation in medial PFC compared with the neutral pictures.[35]

Many other studies that have used PET to measure regional cerebral blood flow or metabolism have observed emotion-related alterations in PFC activation. A common method for the experimental production of aversive emotion has been to use anxiety-disordered patients exposed to stimuli that provoke anxiety (e.g. pictures of spiders for spider phobics). Pooling across data from three different anxiety disordered groups (obsessive–compulsive disorder, simple phobia, and post-traumatic stress disorder) Rauch and colleagues[36] found a group of structures commonly activated across these disorders during the experimental provocation of anxiety. Two regions within the PFC were strongly activated across groups: right inferior PFC and right medial orbital PFC. In an fMRI study of symptom provocation among patients with obsessive–compulsive disorder, Breiter and colleagues[37] observed bilateral activation of anterior and posterior orbitofrontal cortex.

Several investigators have used classical aversive conditioning to study the neural substrates of the acquisition and extinction of emotional learning. Most studies have focused on the amygdala and they will be reviewed below. However, in the present context, we note that Hugdahl et al.[38,39] reported a significant increase in widespread zones of the right PFC including the orbitofrontal and dorsolateral cortices and inferior and superior frontal cortices during extinction compared to habituation.

Various studies have reported significant decreases in PFC blood flow associated with the activation of particular emotional states, with induced happiness resulting in a reduction in activation in the right superior PFC and visually induced recall of an aversive emotional episode being associated with a significant reduction in left-sided PFC activation in the region of Broca's area and the operculum.[40,41]

In summary, there is growing consistency between the lesion data on the mood consequences of small unilateral lesions and the findings from neuroimaging studies in supporting the view of right-sided activation in several regions within PFC during the experimental arousal of negative emotion. Less evidence is available on the prefrontal changes associated with positive affect, in part because much of the literature on negative affect is derived from the study of patients with anxiety and mood disorders. Systematic study of comparable subjects who are predisposed to positive affect has never been undertaken though certainly could be based upon available evidence.[31,42] It must be noted that some of the neuroimaging evidence for lateralized changes in PFC activation during emotion is derived from studies that have not rigorously tested the interaction of condition with hemisphere and thus, must be regarded with some caution until additional studies using more appropriate analytic procedures have been performed.

Bechara and colleagues' studies on the ventromedial PFC strongly suggest that this neural sector is involved in the anticipation of future affective consequences because patients with damage to this region fail to generate the normal anticipatory electrodermal responses to affectively salient cues. It will be of great interest in

the future to carefully examine whether asymmetries in the representation of valence are present in this region. The evidence to date is derived from patients with bilateral lesions.

Many theoretical accounts of emotion assign it an important role in guiding action and organizing behavior in a motivationally consistent manner.[43] To accomplish this, it is essential that the organism have some means of representing affect in the absence of immediate elicitors—an affective working memory. It is likely that the PFC plays a crucial role in this process. Damage to specific sectors of the PFC appears to impair a person's ability to sustain emotion and to use it to guide behavior in an adaptive fashion. Note that such damage would not impair immediate reactivity to incentives, but only the capacity to sustain and anticipate such reactions when the immediate elicitors are not present. The ventromedial sector of the PFC is probably most directly involved in the representation of elementary positive and negative states in the absence of immediately present incentives, while the dorsolateral PFC is probably most directly involved in the representation of the goal states toward which these more elementary positive and negative states are directed. This formulation must be tested explicitly in future research.

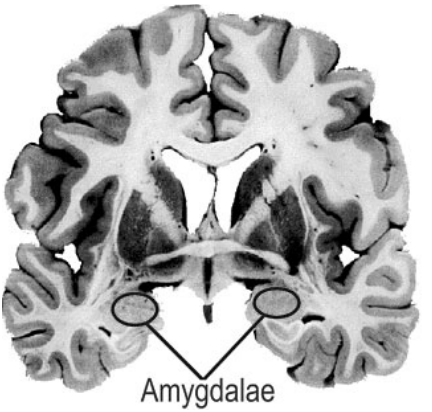

Figure 31.2
Human amygdalae. Coronal section of the human brain indicating the location of the amygdalae (yellow) deep within the temporal lobes. (Adapted from ref. 93.)

Amygdala

A growing body of data from a small group of human patients with discrete lesions in the amygdala highlight the importance of this region for both the perception and production of negative affect and associative aversive learning (see Ref. 7 for general review and Ref. 44 for review of animal studies on the amygdala and emotional memory) (see Fig. 31.2). Adolphs and his colleagues[45,46] have demonstrated that the recognition of facial signs of fear was impaired in patients with bilateral amygdala damage while recognition of other facial expressions was intact. A specific deficit in the recognition of facial expressions of fear in patients with amygdala damage has been demonstrated in two additional studies using a different methodology for the assessment of facial expression recognition.[47,48] It is likely that the deficit in the perception of expressive signs of fear in patients with amygdala damage is not specific to facial expressions since Scott et al.[49] demonstrated a deficit in the recognition of vocalic expressions of fear and anger in a patient with bilateral amygdala damage.

Bechara and colleagues[50] have demonstrated a crucial double dissociation by comparing a patient with selective bilateral amygdala damage to one with selective bilateral hippocampal damage on a conditioning task during which electrodermal measures of affective aversive association were obtained, along with measures of declarative knowledge of the conditioning contingencies. It was found that the patient with amygdala damage was impaired in electrodermal conditioning but showed intact declarative knowledge of the task contingencies while the patient with hippocampal damage and an intact amygdala demonstrated reliable electrodermal condition-

ing but showed no declarative knowledge of the conditioning contingencies. A patient with bilateral damage to both structures was impaired on both sets of measures. Other evidence suggests that declarative memory for complex emotional material is selectively disrupted in patients with bilateral amygdala damage.[51]

Angrilli and colleagues[52] studied the startle responses of a patient with a benign tumor of the right amygdala in comparison with a group of controls. Among control subjects, they replicated the well-known effect of aversive stimuli potentiating startle magnitude. However, in the patient with the right amygdala lesion, no startle potentiation was observed in response to aversive versus neutral stimuli. These data are consistent with the view that the amygdala is crucial for normal negative-affect potentiated startle in humans. In a very recent study that required subjects to make judgements of the trustworthiness and approachability of unfamiliar individuals from facial photographs, patients with bilateral damage to the amygdala judged the unfamiliar individuals to be more approachable and more trustworthy than did control subjects.[53] Collectively, the studies of patients with damage to the amygdala suggest that this structure plays an important role in both the perception and production of certain forms of negative emotion. The extent to which the human amygdala also plays a role in positive affect is unanswered by extant lesion studies. Moreover, the lesion studies need to be complemented by neuroimaging studies that examine activation in the amygdala in intact subjects in response to affective challenges since damage to the amygdala can have functional consequences in territories far removed from the site of the actual lesion.

A growing body of neuroimaging literature using both PET and fMRI have reported on changes in the human amygdala in response to emotional stimuli. These studies are helping to clarify the functional role of the amygdala in various components of emotional processing. However, it is necessary to underline the functional heterogeneity of the amygdala. So significant is this heterogeneity that some anatomists have been led to question whether the amygdala should properly be regarded as a discrete, unitary structure (see Ref. 54 for a compelling statement of this position). Unfortunately, because of its relatively coarse spatial resolution, it is not likely that PET will enable investigators to differentiate among different subnuclei of the amygdala. It is more likely that fMRI will have sufficient spatial resolution, particularly at higher field strengths, to resolve different regions within the amygdala, although there have not yet been attempts to manipulate task variables systematically in order to determine whether differential activation of regions of the amygdala can be detected.

A number of PET and fMRI studies have been performed with patients having one of several different anxiety disorders and examining cerebral blood flow in the amygdala and other brain regions in response to the experimental provocation of anxiety. For example, using PET measures of blood flow, Rauch[55] exposed patients with post traumatic stress disorder to imagery scripts that were designed to activate traumatic memories. These were compared to neutral imagery scripts. Activation of the right amygdala was found in this study and remained equally significant when compared to a teeth clenching control condition.[56] Breiter et al.[37] used fMRI to examine regional patterns of activation in patients with obsessive–compulsive disorder exposed to idiographically tailored stimuli designed to provoke the patient's symptoms. In response to such stimuli compared with control stimuli, significant bilateral activation of the amygdala was detected. Birbaumer and colleagues[57] reported bilateral amygdala activation in response to neutral facial expressions (compared with a resting baseline condition) in a group of male social phobics. The amygdalar activation in this group was comparable in magnitude to that elicited by an aversive odor. In a group of controls, they observed amygdalar activation to the aversive odor but not to the neutral faces.

Consistent with the lesion data are studies that find specific activation of the amygdala in response to faces depicting expressions of fear. Using PET, Morris et al.[58] demonstrated that fear faces elicit significantly greater blood flow in the amygdala compared with happy faces. Moreover, the intensity of fear displayed in faces was systematically related to increases in blood flow in the left amygdala. In a subsequent reanalysis of these data, Morris and colleagues[59] found that increased blood flow in the amygdala predicted increased blood flow in extrastriate visual cortex during fear but not during happy presentations. These findings indicate that the pattern of functional connectivity between these regions is altered as a function of emotional expression condition.

Activation of the amygdala in response to fear faces has also been found with fMRI. Because of the better time resolution of fMRI, Breiter et al.[60] were able to examine the temporal changes in amygdalar activation and found that the response to fear faces showed rapid habituation. Phillips et al.[61] replicated this finding and further demonstrated that disgust faces failed to activate the amygdala. Rather, in response to disgust faces, subjects showed activation in a region implicated in processing gustatory stimuli—the anterior insula. Recently, Whalen and colleagues[62] demonstrated activation of the amygdala in response to fear faces that were not consciously perceived. They achieved this by masking the fear faces with neutral faces that were presented contiguously with the offset of the fear faces. Happy faces masked in this way showed significantly less amygdala activation compared with masked fear faces.

Using either pleasant and unpleasant pictures or happy and sad faces accompanied by instructions to generate the emotion depicted on faces, while measuring regional blood flow with PET, investigators have found activation in the left amygdala during unpleasant compared to neutral pictures[63] and during sad compared with happy mood generation.[64] In a conceptual replication of this latter study, the same group used fMRI to detect regional brain activation and again found activation of the left amygdala but this time to both sad and happy conditions compared to the neutral condition.[65] Using fMRI, we presented pleasant and unpleasant pictures and compared them to neutral pictures and found that only unpleasant pictures activated the amygdala.[66,67] LaBar et al.[68] found bilateral activation in the amygdala in response to both unpleasant and pleasant stimuli compared to neutral stimuli. Importantly, the LaBar et al. study included erotic nudes in their positive picture set while our studies did not. It may well be that the inclusion of these stimuli made a crucial difference in the activation of the amygdala during the positive condition. We will return to this issue at the end of this section.

Two recent fMRI studies of classical aversive conditioning[69,70] have reported bilateral amygdala activation during the early phases of acquisition which then habituates rapidly. In a recent PET study of conscious and unconscious conditioning, Morris and colleagues[71] compared the responses to backwardly masked angry faces that had been paired with noise to consciously perceived angry faces paired with noise. Masked presentations of the conditioned angry face elicited activation in the right amygdala while unmasked presentations of the same face elicited activation in the left amygdala.

Several others types of manipulations have been found to enhance neural activity in the amygdala. Exposing normal individuals to an unsolvable anagram task of the sort used to induce learned helplessness produced increased blood flow in the amygdala.[72] Aversive olfactory stimuli were found to produce strong activation in the left amygdala[73] compared to a no odorant control condition, while aversive gustatory stimuli produced activation in the right amygdala.[74]

Individual differences in amygdala activation have been related to various measures of affective style (see Box 31.2).

Box 31.2
The amygdala and affective style

A number of recent studies have examined individual differences in amygdala activation in relation to various features of emotional reactivity and affective style. One of the most striking features of emotion is the profound variability among individuals in the quality and intensity of response to the identical stimulus. Davidson (Ref. a) has outlined a program of future research on affective style that seeks to parse the domain into specific sub-components, with an emphasis on the temporal dynamics of responding. For example, in this scheme, the time required to recover (i.e. return back to baseline) from a negative provocation is an important mechanism governing individual differences in negative affect.

Studies that examine individual differences in amygdala activation and affective style fall into two broad categories. First are studies that examine the correlates of individual differences in baseline blood flow or glucose metabolism in the amygdala. One of the first to perform such an analysis was Drevets and his colleagues (Ref. b) who examined relation between PET measures of resting blood flow and depression severity in a small group of depressed patients. These investigators reported that depressed patients with increased baseline blood flow in the amygdala had higher depression severity ratings. This analysis was based upon a region-of-interest (ROI) created by growing a sphere around a Talairach coordinate for the left amygdala. This approach is likely to include activity from a much larger region than just the amygdala, particularly since the PET data were smoothed to minimize contributions of anatomical variability across subjects in the group analysis. Using MRI coregistration with ROIs drawn on each subject's MRI scan around the amygdala and unsmoothed PET data, we (Ref. c) largely replicated the Drevets et al. (Ref. b) finding in a larger sample of depressed patients using baseline PET measures of regional glucose metabolism (see Figs 31.3 and 31.4A,B) and a psychometrically well-validated measure of dispositional negative affect. Individuals who exhibited elevated levels of glucose metabolism at

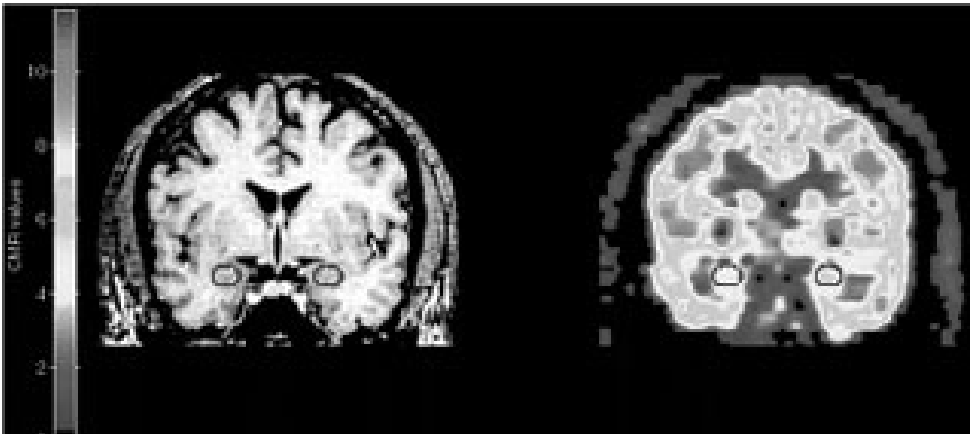

Figure 31.3
Illustration of PET-MRI coregistration and amygdalar RO1 delineation. Representative image planes in coronal section are shown for one participant. The PET image plane is presented besides its corresponding coregistered MRI plane. Units of the PET color scale are in mg/100g/min. (Adapted from Ref. 94.)

Box 31.2
(continued)

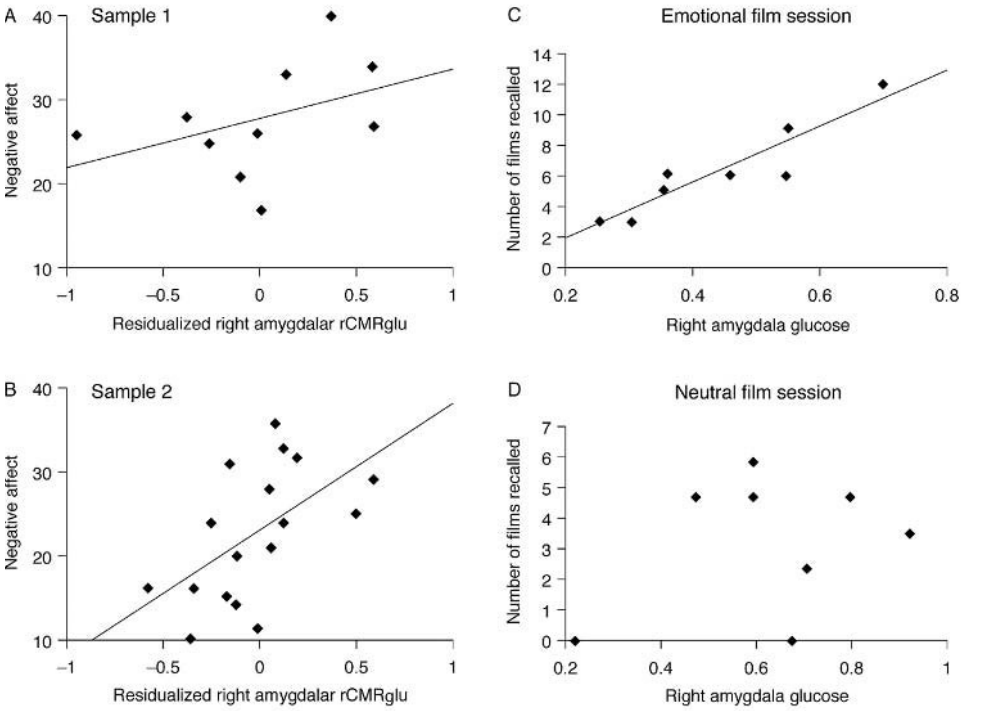

Figure 31.4
Metabolic activity in the right amygdala and individual differences in negative affect. Scatter plots of correlations in depressed groups between dispositional negative affect (assessed with the PANAS Negative Affect Scale—Trait Version (Ref. i) and glucose metabolism in the right amygdala (rCMRglu = regional cerebral metabolic rate for glucose, residualized for global metabolic rate) for two samples (**A, B**) of depressed patients (N = 10 and 17 respectively, tested on different PET scanners). Sample 1, r(8) = 0.41, p = 0.24; Sample 2, r(15) = 0.56, p = 0.02. (Adapted from Ref. 94.) (**C, D**) Scatter plots of correlations in normal subjects between the number of negative emotional films recalled (**C**; $r = 0.93$, $p > 0.01$) and the number of neutral films recalled (**D**; $r = 0.33$, not significant) and metabolic rate in the right amygdala derived from PET during the respective film clips. (Adapted from Ref. 95.)

Box 31.2
(continued)

baseline reported significantly higher levels of dispositional negative affect.

The second type of study examines the relation between individual differences in reactivity of amygdala blood flow or metabolism to an emotional challenge and other behavioral or self-report indices of emotional reactivity. Cahill and colleagues (Ref. d) reported that subjects with higher levels of amygdala metabolic rate in response to negative emotional films showed better free recall of these films three weeks following their presentation. Glucose metabolism in the amygdala showed no relation to recall of neutral film clips (see Fig. 31.4C,D). We recently found that subjects showing greater MR signal change in the amygdala in response to negative compared with neutral pictures reported significantly higher levels of dispositional negative affect on a self-report measure (Ref. e). Fredrikson and his colleagues reported that those subjects showing greater increases in amygdala blood flow (particularly on the right side) detected with PET during extinction compared with habituation in a classical conditioning paradigm also showed greater evidence of electrodermal conditioning (Ref. f). LaBar et al. conceptually replicated this finding using fMRI (Ref. g), though in this study, electrodermal measures were obtained during a separate session 1–3 months following the fMRI data collection. Despite the time interval between sessions, a significant positive correlation was obtained between MR signal change in the amygdala during conditioning and magnitude of skin conductance responses obtained 1–3 months later.

Using a pharmacological challenge procedure with the anesthetic procaine, Ketter and colleagues compared those individuals who reported euphoric versus dysphoric responses to the challenge (Ref. h). Subjects with the negative affective response to the procaine had significantly greater activation of the amygdala as detected by PET. Moreover, amygdala blood flow correlated positively with fear and negatively with euphoria on self-report measures of emotional intensity.

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Issues Raised by the Amygdala Findings

The data reviewed above clearly implicate the amygdala as an important site for the control of emotion in the human brain. However, the results also raise many questions about the precise nature of the role this region plays in emotion. Here we wish to highlight three major issues.

(1) *Affect in general, negative affect in particular, or fear most specifically?* The existing data are equivocal on this issue. Many studies find greater amygdala activation in response to negative elicitors compared with positive elicitors. Some studies find that the greater the reported or autonomically displayed negative affect, the greater the activation in the amygdala. Other studies have found amygdala activation in response to both negative and positive emotional challenges. For example, LaBar et al.[68] observed bilateral MR signal increases in the amygdala in response to both negative and positive pictures compared with neutral pictures. As we noted above, this latter study included erotic nudes among the positive picture set while our study,[67] which revealed amygdala activation only in response to negative versus neutral pictures, did not. It is noteworthy that the Breiter et al. fMRI study of the effects of cocaine in cocaine addicts (Ref. 75, discussed in more detail below) found significant deactivation of the amygdala during cocaine-induced "highs."

The studies that have compared activation of the amygdala in response to facial expressions depicting different emotions have consistently found the greatest activation of the amygdala in response to fear faces. It is conceivable that these data could be subsumed under a model of amygdala function that assigned a premium role to the detection of ambiguity (see Ref. 76 for a discussion of this theory). On this view, the preferential activation of the amygdala in response to fear compared with angry faces, for example, is explained by the fact that angry faces provide information about the presence of threat as well as the source of threat while fear faces provide information about the former but not the latter. Erotic stimuli may be interpreted as ambiguous for many different reasons (e.g. they might automatically elicit approach, but also could activate avoidance responses because of moral considerations etc.). Inconsistent with this view, however, are the data on the recognition of vocal affect in a patient with bilateral amygdala damage which indicated impaired recognition of both fear and anger.[49] What is required is to manipulate the valence of emotion while carefully matching conditions on variables that might be associated with ambiguity. Alternatively, ambiguity can be parametrically varied (e.g. by altering the probability of a shock appearing during the presence of a particular CS) to determine if amygdala activation tracked variations in manipulated ambiguity.

(2) *Left, right or both?* During the experimental arousal of negative affect, some studies report changes in left amygdala activation,[65] others report changes in right amygdala activation,[55] while still others report bilateral changes.[66] Adding to this complexity is the recent report by Morris et al.[71] who observed right amygdala activation to unconsciously presented aversively conditioned angry faces and left amygdala activation to conscious presentations of the same face. It is essential to stress the importance of proper statistical analysis of laterality effects in neuroimaging studies (see Box 31.1 and Ref. 77 for a more in depth discussion). Until these procedures are followed more rigorously, it will not be possible to sort out whether asymmetric activation in the amygdala is associated with different patterns of affective response.

(3) *Can the amygdala be treated as a homogeneous structure?* Of course, the obvious answer to this question is a resounding no, yet most investigators continue to treat this region as if it were a unitary structure. Unfortunately, this state of affairs is not likely to change until studies are

completed on MRI scanners with field strengths higher than conventional scanners (i.e. more than 2T). When such studies are performed, it is likely that the region of the amygdala that is activated in response to faces will differ from the region activated during the expression of a negative emotional response. Uneven sampling of the amygdala and partial volume effects with other adjacent structures due to the relatively coarse resolution of most fMRI and all PET studies probably accounts for some of the variability among studies. Future fMRI studies at higher field strength hold great promise in elucidating the functional specialization of different amygdaloid regions.

Other Brain Regions

While most of the extant literature has focused on PFC and amygdala as two critical components of a circuit involved in human emotion processing, many studies have offered evidence of other brain regions participating in affective responding. One key region that has emerged mostly from behavioral, lesion and electrophysiological data is posterior right hemisphere involvement in both the perception of emotional information as well as in the arousal component of emotion. This literature is not reviewed here because it has been recently reviewed elsewhere.[78–80] In addition, precise anatomical specification of the locus of these effects is not available because the methods that have been used for their study provide only course localizing information. Here we briefly review data on three other regions that have been most consistently implicated in emotional processing in recent neuroimaging studies.

Ventral Striatum

Breiter et al.[75] examined the effects of cocaine infusion in cocaine addicts on MR signal change in comparison to saline infusion. They found activation in a distributed circuit that included cortical and subcortical regions. Of note is the strong activation observed in regions of the ventral striatum which includes the caudate, putamen and the nucleus accumbens. Activation in this latter region is consistent with a large corpus of non-human data demonstrating the critical role played by the mesolimbic dopaminergic pathway in positive affect and addictive behaviors.[81,82] Stein et al.[83] in the first fMRI study of the effects of nicotine on regional brain activation in cigarette smokers also found activation of the nucleus accumbens during infusion of nicotine compared with saline. In our PET study described above that used pleasant and unpleasant pictures in an extended picture paradigm,[33] we observed activation in a region including the nucleus accumbens during the picture-induced positive affect.

Anterior Cingulate

Many neuroimaging studies that have compared an emotional to a neutral condition have reported activation in the anterior cingulate cortex (ACC). Theoretical and empirical analyses suggest that the ACC plays an important role in aspects of attentional processing.[84] In a recent study that was designed to better understand the role of the ACC in emotion, Lane et al.[63] exposed subjects to emotional pictures under two conditions: during one condition subjects were asked to attend to their subjective emotional responses and indicate whether the picture evoked a pleasant, unpleasant or neutral feeling, while in a second condition (during exposure to similar pictures), they were asked to indicate whether the picture depicted a scene that was indoors, outdoors or either. They observed a significant focus of activation in the ACC during the condition requiring attention to subjective emotional responses compared with the condition requiring attention to the context of the stimulus (see also Ref. 85).

Insular Cortex

Activation of the insular cortex has also been reported in many neuroimaging studies that have manipulated emotion, ranging from studies of symptom provocation in anxiety-disordered patients[86] to studies of emotion activation in normal individuals[34] and to pharmacologically manipulated emotion.[75] The fact that a very diverse range of manipulations produce activation in the insular cortex is consistent with the idea that this cortical territory plays a critical role in visceral representation.[87] The insular cortex receives afferents from several major autonomic regions and sends efferents to a number of brain regions that play a critical role in regulating autonomic responses that accompany emotion including the central nucleus of the amygdala and the lateral hypothalamus. The insular cortex is topographically organized and includes a major zone dedicated to gustatory processing. This latter fact is probably responsible for the significant insular activation detected with fMRI in response to disgust faces,[61] which can be understood as signifying distasteful stimuli (see recent discussions by Rozin and Young et al.[88,89]).

To summarize the findings from these other brain regions, activation of ventral striatum has most consistently appeared in studies that manipulated positive affect. This region is richly innervated by dopaminergic neurons and a recent human PET study has found increases in dopamine turnover in this general region during the playing of an enjoyable video game.[90] The mesolimbic dopamine system has been implicated in incentive reward motivation[13] and it is likely that this system plays an important role in what Davidson[91] has previously described as "pre-goal attainment positive affect," that form of positive affect that arises as one moves progressively closer toward a desired goal.

The anterior cingulate region has been reported to be activated in most neuroimaging studies of emotion when an emotion condition is compared with a neutral control condition. This region might play an important role in mediating the attentional effects of affective arousal. When emotion is evoked it is usually attentionally salient. It would be informative in future research to compare emotion evoked non-consciously versus consciously[71] and determine if activation of the ACC occurs during the latter but not the former.

Based upon its known inputs and outputs, activation of the insular cortex during emotion is probably associated with the autonomic changes that typically occur when emotion is evoked. However, from the extant evidence, we do not know if the insular activation is primarily a function of visceral afferent feedback or rather is produced by the insular cortex issuing efferent commands for autonomic change. The use of peripheral beta blockers to attenuate peripheral autonomic activity during emotional arousal[92] in conjunction with neuroimaging would permit the determination of whether insular activation was primarily driven by visceral feedback to the insular or rather insular participation in the efferent control of autonomic function.

Conclusions

Just as cognitive neuroscience has taught us the importance of decomposing global cognitive constructs into more elementary constituents whose neural substrates could be identified, so too modern research in affective neuroscience underlines the importance of identifying specific subcomponents of emotion whose anatomical bases may be examined. In this article we have relied on three primary sources of data to make inferences about the circuitry underlying positive and negative emotion in the human brain: lesion, PET and fMRI studies. This corpus of work underlines the importance of several interconnected regions comprising a circuit for human affective responding: the ventromedial and dorsolateral PFC, amygdala, ventral striatum, anterior cingulate and insular cortex. Each of these regions appears to play a separate function in emotion

although very few studies have been designed to manipulate these emotion subcomponents specifically in order to demonstrate rigorously such specificity. Evidence for the lateralization for emotional valence was also summarized, which supports the view of regions of the right PFC specifically implementing components of aversive emotional responding. As we develop more reliable methods to investigate emotion in the laboratory and to study its interaction with various cognitive processes, these procedures, combined with neuroimaging technologies, will allow us to address questions about brain mechanisms in ways that were previously approachable only through research on non-human species. This new information will provide a compelling foundation for theoretical advances in the basic understanding of the constituents of emotion and for practical advances in the treatment of affective dysfunction.

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