DEPRESSION: Perspectives from Affective Neuroscience

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■ **Abstract**   Depression is a disorder of the representation and regulation of mood and emotion. The circuitry underlying the representation and regulation of normal emotion and mood is reviewed, including studies at the animal level, human lesion studies, and human brain imaging studies. This corpus of data is used to construct a model of the ways in which affect can become disordered in depression. Research on the prefrontal cortex, anterior cingulate, hippocampus, and amygdala is reviewed and abnormalities in the structure and function of these different regions in depression is considered. The review concludes with proposals for the specific types of processing abnormalities that result from dysfunctions in different parts of this circuitry and offers suggestions for the major themes upon which future research in this area should be focused.

CONTENTS

INTRODUCTION

Affective neuroscience is the subdiscipline of the biobehavioral sciences that examines the underlying neural bases of mood and emotion. The application of this body of theory and data to the understanding of affective disorders is helping to generate a new understanding of the brain circuitry underlying these disorders.

Moreover, parsing the heterogeneity of these disorders on the basis of known circuits in the brain is providing a novel and potentially very fruitful approach to subtyping that does not rely on the descriptive nosology of psychiatric diagnosis but rather is based upon more objective characterization of the specific affective deficits in patients with mood disorders. At a more general level, this approach is helping to bridge the wide chasm between the literatures that have focused on normal emotion and the disorders of emotion. Historically, these research traditions have had little to do with one another and have emerged completely independently. However, affective neuroscience has helped to integrate these approaches into a more unified project that is focused upon the understanding of normal and pathological individual differences in affective style, its constituent components, and their neural bases (see e.g., Davidson et al. 2000a, Davidson 2000).

Affective neuroscience takes as its overall aim a project that is similar to that pursued by its cognate discipline, cognitive neuroscience, but focused instead on affective processes. The decomposition of cognitive processes into more elementary constituents that can then be studied in neural terms has been remarkably successful. We no longer query subjects about the contents of their cognitive processes because many of the processes so central to important aspects of cognitive function are opaque to consciousness. Instead, modern cognitive scientists and neuroscientists have developed laboratory tasks to interrogate and reveal more elementary cognitive function. These more elementary processes can then be studied using imaging methods in humans, lesion methods in animals, and the study of human patients with focal brain damage. Affective neuroscience approaches emotion using the same strategy. Global constructs of emotion are giving way to more specific and elementary constituents that can be examined with objective laboratory measures. For example, the time course of emotional responding and the mechanisms that are brought into play during the regulation of emotion can now be probed using objective laboratory measures. These constructs may be particularly important for understanding mood disorders because patients with depression may suffer from abnormalities in emotion regulation and persistence of negative affect. Patients with such abnormalities may differ from those whose primary deficit may be in reactivity to positive incentives.

Previously constructs such as emotion regulation have mostly been gleaned from self-report measures whose validity has been seriously questioned (e.g., Kahneman 1999). Whereas the phenomenology of emotion provides the subject with critical information that helps guide behavior, it may not be a particularly good source for making inferences about the processes and mechanisms that underlie emotion and its regulation. Though it is still tempting and often important to obtain measures of the subject's conscious experience of the contents of their emotional states and traits, these no longer constitute the sole source of information about emotion.

Because there are recent reviews of the basic literature on the circuitry underlying emotion and emotion regulation (e.g., Davidson & Irwin 1999; Davidson et al. 2000a,d; Rolls 1999), these data are not systematically reviewed in this chapter. We emphasize studies that have been published in the past 3 years because

two recent reviews cover much of the earlier literature (Davidson et al. 1999, Drevets 1998). We wish to underscore at the outset that one of the crucial issues that plagues research in this area is the heterogeneity of mood disorders. Depression may arise from a multitude of proximal causes and whereas the broad symptoms share a certain similarity, the underlying mechanisms may differ. For example, some depressed patients have pervasive symptoms of negative affect and anxiety as part of their symptom cluster and may suffer from an inability to recover from a stressful event. Other patients may exhibit a pervasive lack of positive affect as their primary dysfunction. For these patients, positive incentives do not possess reinforcing potential. These examples illustrate pathways into depression and are likely mediated by different neural circuits despite the fact that they culminate in a set of symptoms that are partially shared. It is apparent that traditional methods for parsing heterogeneity on the basis of descriptive phenomenology are not yielding clean separation of underlying neural circuitry. For example, the melancholic versus nonmelancholic distinction does not systematically reveal differences in neural correlates (see below). Recommendations for moving beyond phenomenology and toward a more objective, laboratory-based parsing of affective processing abnormalities are provided throughout this chapter.

We have three broad goals for this chapter: (*a*) to review the functional role of the prefrontal cortices, anterior cingulate, hippocampus, and amygdala in affect and emotion regulation [see Figure 1 for a depiction of these structures and their locations]; (*b*) to review the functional and structural abnormalities that have been found in these regions in depression; (*c*) based upon the first and second goals above, to advance hypotheses about symptom clusters that may arise as a consequence of dysfunctions in specific regions and to offer suggestions for different ways of parsing the heterogeneity of depression in ways that more directly honor the circuitry of emotion and emotion regulation in the brain.

THE CIRCUITRY OF EMOTION

Prefrontal Cortex

FUNCTIONAL AND ANATOMICAL CONSIDERATIONS FOR UNDERSTANDING ITS ROLE IN AFFECT AND DEPRESSION   Abnormalities in activation of prefrontal regions in depression have been reported more frequently than for any other brain region, mostly in the direction of decreased bilateral or predominantly left-sided activation (Davidson et al. 1999, George et al. 1994). Miller & Cohen (2001) have recently outlined a comprehensive theory of prefrontal function based upon non-human primate anatomical and neurophysiological studies, human neuroimaging findings, and computational modeling. The core feature of their model holds that the prefrontal cortex (PFC) maintains the representation of goals and the means to achieve them. Particularly in situations that are ambiguous, the PFC sends bias signals to other areas of the brain to facilitate the expression of task-appropriate

responses in the face of competition with potentially stronger alternatives. In the affective domain we often confront situations in which the arousal of emotion is inconsistent with other goals that have already been instantiated. For example, the availability of an immediate reward may provide a potent response alternative that may not be in the best service of a person's overall goals. In such a case the PFC is required to produce a bias signal to other brain regions that guide behavior toward the acquisition of a more adaptive goal, which in this case would entail delay of gratification.

Affect-guided planning and anticipation that involves the experience of emotion associated with an anticipated choice is the hallmark of adaptive, emotion-based decision making that has repeatedly been found to become impaired in patients with lesions of ventromedial PFC (Damasio 1994). Affect-guided anticipation is most often accomplished in situations that are heavily laden with competition from potentially stronger alternatives. In such cases in particular, we would expect PFC activation to occur. Certain subtypes of depression may be caused by abnormalities of affect-guided anticipation. For example, the failure to anticipate positive incentives and direct behavior toward the acquisition of appetitive goals are symptoms of depression that may arise from abnormalities in the circuitry that implements positive affect-guided anticipation. Our laboratory has contributed extensively to the literature on asymmetries in PFC function associated with approach- and withdrawal-related emotion and mood (e.g., Davidson & Irwin 1999, Davidson et al. 2000a). In this context we suggest that left-sided PFC regions are particularly involved in approach-related, appetitive goals. The instantiation of such goals, particularly in the face of strong alternative responses, requires left-sided PFC activation and hypoactivation in these circuits has been linked to depression. Right-sided PFC regions, alternatively, are hypothesized to be particularly important in the maintenance of goals that require behavioral inhibition and withdrawal in situations that involve strong alternative response options to approach. The prototype of such a process has recently been captured in several neuroimaging studies that involve variants of a go/no go task in which a dominant response set is established to respond quickly, except in those trials on which a cue to inhibit the response is presented. Two recent studies using event-related functional magnetic resonance imaging (fMRI) have found a lateralized focus of activation in the right lateral PFC (inferior frontal sulcus) to cues that signaled response inhibition that were presented in the context of other stimuli toward which a strong approach set was established (Garavan et al. 1999, Konishi et al. 1999).

Depressed individuals with hypoactivation in certain regions of the PFC may be deficient in the instantiation of goal-directed behavior and in the overriding of more automatic responses that may involve the perseveration of negative affect and dysfunctional attitudes. Such deficits would be expected to be unmasked in situations in which decision-making is ambiguous and in which the maintenance of goal-directed behavior is required in the face of potentially strong alternative responses. As we argue below, when the strong alternative responses involve affect, which they often do, the ventromedial PFC is particularly implicated.

Recent neuroimaging and electrophysiological studies suggest that the orbital and ventral frontal cortex may be especially important for the representation of rewards and punishments, and different sectors within this cortex may emphasize reward versus punishment (Kawasaki et al. 2001, O'Doherty et al. 2001). In particular, a left-sided medial region of the orbital frontal cortex (OFC) appears responsive to rewards, whereas a lateral right-sided region appears responsive to punishments (O'Doherty et al. 2001). Kawasaki and colleagues (2001) recorded from single units in the right ventral PFC of patients with implanted depth electrodes for presurgical planning. They found these neurons in healthy tissue to exhibit short-latency responses to aversive visual stimuli. Such studies provide important clues regarding the circuitry that might be most relevant to understanding abnormalities associated with depression. It will be important in the future to evaluate the performance of depressed patients on a task of this kind with neuroimaging. Differential responsivity to rewards versus punishments has been found behaviorally in two studies in our laboratory (Henriques et al. 1994, Henriques & Davidson 2000). In particular, whereas normal individuals exhibited systematic modification of response bias to monetary reward, depressed patients failed to show such changes but did show response bias shifts in response to monetary punishment. On the basis of these findings, we predict that left medial OFC would be hyporesponsive to manipulations of reward in such patients, whereas right lateral OFC activation to punishment would either be normal or perhaps accentuated.

PREFRONTAL CORTEX IN DEPRESSION: THE FINDINGS   Consistent with prior literature, recent reports have documented decreased activation in both dorsolateral and dorsomedial PFC as well as the pregenal region of the anterior cingulate gyrus in patients with major depressive disorder (see Drevets 1998 for comprehensive review). The reduction in activation in this latter region, particularly on the left side, appears to be at least partially a function of a reduction in the volume of gray matter as revealed by magnetic resonance imaging-derived morphometric measures (Drevets et al. 1997). Consistent with the notion that the metabolic reduction found in this region is at least partially a function of the volume reduction, Drevets et al. (1997) have reported that remission of symptoms associated with successful treatment is not accompanied by a normalization of activation in this area.

This general decrease in dorsolateral PFC and in the pregenual region of the anterior cingulate cortex (ACC) tends to be accompanied by an increase in other regions of the PFC, particularly in the ventrolateral and orbital (lateral and medial) zones. Treatment studies have found that activation in dorsolateral PFC, particularly on the left side, increases following successful antidepressant treatment (Kennedy et al. 2001). Less consistent are findings for ventrolateral and orbital PFC regions. Some studies have found increases in these regions (Kennedy et al. 2001), but others have reported decreases (e.g., Brody et al. 1999, Mayberg et al. 1999).

As suggested above, recent reports of anatomical differences in the PFC are of critical import to any claims made about functional differences between depressed patients and normal controls. Consistent with earlier work conducted by Coffey

et al. (1993), who found a sample of 48 depressed inpatients to have frontal lobe volumes that were 7% smaller than 76 nonpsychiatric controls, Drevets et al. (1997) reported that unipolar and bipolar depressives with a family history of mood disorders showed a 48% and 39% reduction in subgenual PFC volume, respectively. In a postmortem study by the same group (Öngür et al. 1998b), glial cell number was significantly reduced in subgenual PFC in both unipolar (24%) and bipolar (41%) patients with a family history of major depressive disorder (MDD). No significant effects were observed for nonfamilial MDD or bipolar disorder.

Rajkowska (2000) has further examined alterations in neuronal and glial histopathology in postmortem brains of patients who suffered from mood disorders. She and her colleagues found that left prefrontal cortices (no other brain areas were examined) of MDD subjects had decreases in cortical thickness, neuronal size, and neuronal and glial densities in upper cortical layers (II-IV) of left rostral OFC; decreases in neuronal size and glial densities in lower cortical layers (V-VI); and decreases in neuronal and glial size and density in supra- and infragranular layers. Of note, they found a 12–15% reduction of cortical thickness in the lateral OFC. Furthermore, they argued that the 22–37% reduction in density of large neurons and 6–27% increase of small neurons in the rostral OFC and dorsolateral PFC (DLPFC) may implicate cell atrophy rather than cell loss as the mechanism for the reduced cortical volume seen in depression. Similar results were observed in the left DLPFC of bipolar patients. These brains were characterized by a 16–22% reduction in neuronal density in layer III, a 17–30% reduction in pyramidal cell density in layers III and V, and a 19% reduction in glial density in sublayer IIIc. The fact that these anatomical differences in the brain of patients with mood disorders might account for some of the functional differences noted by Drevets et al. (1997) does not in itself provide any direct measures of causal influence. Longitudinal studies of patients at risk for mood disorders are needed to ascertain whether these structural differences are present prior to the onset of a depressive episode. Heritable factors can be examined by studying monozygotic twins discordant for mood disorders to ascertain whether the anatomical abnormalities are found in the affected twin only.

The common observation in electroencephalographic (EEG) studies of an altered pattern of asymmetric activation in anterior scalp regions in the direction of reduced left relative to right activation in depressed or dysphoric individuals has also been replicated several times in recent years (Bell et al. 1998, Bruder et al. 1997, Debener et al. 2000, Gotlib et al. 1998, Pauli et al. 1999, Reid et al. 1998). However, it should be noted that this asymmetry is not invariably found (e.g., Kentgen et al. 2000, Reid et al. 1998). Reid et al. and Davidson (1998) have discussed various methodological and conceptual issues related to the inconsistencies in the literature. One of the most important of these issues concerns the manner in which statistical tests of the hypothesized group difference in frontal asymmetry are conducted. In the Reid et al. report an analysis of variance (ANOVA) was conducted on the asymmetry scores (log right minus log left alpha power; higher numbers on

this index reflect greater relative left-sided activation) (see Davidson et al. 2000b for discussion of EEG recording procedures) with group and site as factors. The site factor was comprised of asymmetry scores from several sites in both anterior and posterior scalp regions. Reid et al. required that the group X site interaction reach significance. The problem with this approach, as noted by Davidson (1998), is that right-sided parietal activation has been reported to be associated with elevations in anxiety (Heller & Nitschke 1998, Davidson et al. 2000c), and of course, many depressed subjects have elevations in anxiety as part of their symptom picture. Thus, a main effect for group rather than a group X site interaction might be expected for depressed subjects with some comorbid anxiety symptoms. Also important is the nature of the control group utilized in these studies. Some studies have used normal control groups that have been screened for lifetime history of psychopathology (e.g., Henriques & Davidson 1991), whereas others have used a more heterogeneous group of controls (e.g., Reid et al. 1998).

Finally, the temporal stability of electrophysiological measures of asymmetric anterior activation may differ in depressed patients relative to controls. Debener et al. (2000) recently confirmed our original observations (Schaffer et al. 1983, Henriques & Davidson 1991) of greater relative right-sided frontal activation in depressed patients compared with controls using data that were averaged across two recording sessions separated by 2–4 weeks. In addition, Debener et al. (2000) confirmed our report of reliable test-retest stability in electrophysiological measures of anterior scalp activation asymmetries (Tomarken et al. 1992). However, Debener et al. also reported that the test-retest stability for depressed patients was poor and suggested that another feature of prefrontal activation asymmetry that marks depression is increased variability. This suggestion, as well as the other procedural and methodological issues noted above, requires careful study in the future.

In an important extension of the work on electrophysiological asymmetries, Bruder and his colleagues (Bruder et al. 2001) examined whether brain electrical asymmetry measures obtained during a pretreatment period predicted response to a selective serotonin reuptake inhibitor (SSRI) treatment. They found that among women in particular, the treatment responders had significantly less relative right-sided activation compared with the nonresponders, though this effect was present in both anterior and posterior scalp regions. Based upon the role of right prefrontal regions in components of negative affect (Davidson 2000) and right posterior regions in arousal and anxiety (Heller & Nitschke 1998), these findings imply that those subjects with global right-activation who would be expected to have symptoms of negative affect and anxious arousal are least likely to show improvements with SSRI treatment.

Anterior Cingulate Cortex

FUNCTIONAL AND ANATOMICAL CONSIDERATIONS FOR UNDERSTANDING ITS ROLE IN AFFECT AND DEPRESSION   Several theories have proposed that the anterior cingulate cortex (ACC) acts as a bridge between attention and emotion (Devinsky

et al. 1995, Ebert & Ebmeier 1996, Mayberg 1997, Vogt et al. 1995). In their re-cent review, Thayer & Lane (2000) described the ACC as "a point of integration for visceral, attentional, and affective information that is critical for self-regulation and adaptability" (p. 211). In light of its anatomical connections (see below), the ACC appears well equipped for assessing and responding to the behavioral significance of external stimuli. Critical roles of the ACC in selective attention (i.e., prioritizing incoming information), affect, and specific characteristic mammalian social be-haviors have been described (Devinsky et al. 1995, Vogt et al. 1992). However, in order to fully understand the role of the ACC in psychopathology, affective states, and emotional processing, it is critical to recognize that the ACC is far from being a functionally homogeneous region, and at least two subdivisions can be discerned (Devinsky et al. 1995, Vogt et al. 1992, 1995). The first, referred to as the affect subdivision, encompasses rostral and ventral areas of the ACC (Brodmann's areas 25, 32, 33, and rostral area 24). The second, referred to as the cognitive subdivi-sion, involves dorsal regions of the ACC (caudal area 24′ and 32′ and cingulate motor area). The affect subdivision possesses extensive connections with limbic and paralimbic regions—such as the amygdala, nucleus accumbens, OFC, peri-aqueductal grey, anterior insula, and autonomic brainstem motor nuclei—and is assumed to be involved in regulating visceral and autonomic responses to stressful behavioral and emotional events, emotional expression, and social behavior. Ow-ing to its strong connections with the lateral hypothalamus, the subgenual ACC Brodman's area 25 (BA 25) is considered the most important region within the frontal cortex for regulating autonomic function (Öngür et al. 1998a).

Conversely, the cognitive subdivision is intimately connected with the DLPFC (BA 46/9), posterior cingulate, parietal cortex (BA 7), supplementary motor area, and spinal cord and plays an important role in response selection and processing of cognitively demanding information. In functional neuroimaging studies, evidence suggesting a functional differentiation between ventral (affective) and dorsal (cog-nitive) ACC subdivisions is emerging (Bush et al. 1998, 2000; Whalen et al. 1998) (see Figure 2).

From a functional perspective, activation of the cognitive subdivision of the ACC has been reported during interference between competing information (Pardo et al. 1990), visual attention (Nobre et al. 1997), monitoring of cognitive (Carter et al. 2000, MacDonald et al. 2000) and reward-related (Rogers et al. 1999) con-flicts, task difficulty (Paus et al. 1997), and increased risk-associated outcome uncertainty (Critchley et al. 2001), among other experimental manipulations. A common denominator among these experimental conditions is that they all re-quired modulation of attention or executive functions and monitoring of competi-tion (Bush et al. 2000). Cohen and colleagues (Carter et al. 1999, 2000; Miller & Cohen 2001) have emphasized the role of the ACC in conflict monitoring. These authors proposed that the ACC may serve an evaluative function, reflecting the degree of response conflict elicited by a given task. Conflict occurs when two or more possible task-related decisions compete with or interfere with each other. According to the "competition monitoring hypothesis," the cognitive subdivision of the ACC monitors conflicts or crosstalk between brain regions. If a signal of

competition emerges, this output signals the need for controlled processing. The DLPFC (BA 9) is assumed to be critical for this form of controlled processing, in that it represents and maintains task demands necessary for such control and inhibits (see e.g., Garavan et al. 1999) or increases neural activity in brain regions implicated in the competition. Thus, dorsal ACC activation leading to a call for further processing by other brain regions may represent a mechanism for effortful control. Activation of the affective subdivision of the ACC has been reported during various emotional states and manipulations (for reviews, see Reiman 1997, Bush et al. 2000; see also Figure 2). What could be a common denominator underlying activation of the rostral/ventral ACC in such disparate experimental conditions, such as pain, classical conditioning, transient mood, primal affect, Stroop task, and perceiving facial expressions, all of which have been reported in the literature? A possible answer to this question is that the affective subdivision of the ACC may be critical for assessing the presence of possible conflicts between the current functional state of the organism and incoming information with potentially relevant motivational and emotional consequences. This suggestion is based on the observation that the affective subdivision of the ACC is involved in behaviors characterized by monitoring and evaluation of performance, internal states, and presence of reward or punishment, which often require change in behavior.

Evidence suggests that ACC activation may be present when effortful emotional regulation is required in situations in which behavior is failing to achieve a desired outcome or when affect is elicited in contexts that are not normative, which includes most laboratory situations (Bush et al. 2000, Ochsner & Barrett 2001). Similarly it is not surprising that the ACC is one of the most consistently activated regions in patients with different anxiety disorders, such as obsessive compulsive disorder (Breiter et al. 1996, Rauch et al. 1997), simple phobia (Rauch et al. 1995), and posttraumatic stress disorder (Rauch et al. 1996, Shin et al. 1997), in which conflicts between response tendencies and environments are prominent. Interestingly, psychosurgical lesions of the ACC have been used as a treatment for mood and anxiety disorders (e.g., Baer et al. 1995; for review, see Binder & Iskandar 2000), possibly because of a reduction of conflict monitoring and uncertainty that otherwise characterize these psychiatric conditions.

ANTERIOR CINGULATE CORTEX IN DEPRESSION: THE FINDINGS   In major depression, decreased ACC activation relative to controls has been repeatedly reported. In single photon emission computed tomography studies, decreased regional cerebral blood flow in the left (Curran et al. 1993, Mayberg et al. 1994) or right (Ito et al. 1996) ACC has been found in medicated depressed unipolar patients compared with controls. Decreased ACC activation has been replicated with positron emission tomography (PET) (Bench et al. 1992, Drevets et al. 1997, George et al. 1997, Kumar et al. 1993) and fMRI (Beauregard et al. 1998) techniques. Interestingly, as shown in Figure 2, the region of the ACC found to be hypoactive in major depression (dorsal ACC: dorsal region of areas 32, 24′, 32′) appears to be different from the one found to be hyperactive in eventual treatment responders (ventral

and rostral ACC, including pregenual areas 24 and 32). Whereas the state of being depressed is associated with reduced dorsal ACC activity (see above), remission has been characterized by increased activity in the same region (Bench et al. 1995, Buchsbaum et al. 1997, Mayberg et al. 1999). Similarly the increased activity in the rostral ACC characteristic of treatment responders (Mayberg et al. 1997; Ebert et al. 1991; Pizzagalli et al. 2001; Wu et al. 1992, 1999) has been shown to normalize (i.e., decrease) in the same subjects after sleep deprivation (Wu et al. 1999, Smith et al. 1999). Based on these findings, recent neurobiological models of depression have highlighted the role of the ACC in the pathogenesis of depression and in the manifestation of its symptomatology (Drevets 2001, Ebert & Ebmeier 1996, Mayberg 1997).

Based on the functional neuroimaging and animal literature reviewed above, it is conceivable to postulate that (*a*) hypoactivation in dorsal regions of the ACC (BA 24′, 32′) may be associated with impaired modulation of attention or executive functions and impaired monitoring of competition among various response options; and (*b*) hypoactivation in ventral regions of the ACC (BA 24, 32) may be associated with blunted conscious experience of affect, hypoarousal, anhedonia, reduced coping potential in situations characterized by uncertainty, conflict, and expectancy violation between the environment and one's affective state. Whereas future studies will need to specifically test these assumptions, recent findings are in good agreement with some of them. In a recent PET study Brody et al. (2001) found that reduction of anxiety/somatization symptoms was associated with decreased activation in the ventral ACC. Conversely, improvements in psychomotor retardation symptoms were associated with increased activation in the dorsal ACC. In a recent combined EEG-PET study using source localization, we observed that melancholic depressed subjects showed evidence of hypoactivation in BA 25 compared with both nonmelancholic depressed and control subjects (D Pizzagalli, T Oakes, CL Larson, AM Hendrick, KA Horras, RJ Davidson, unpublished data).

The interplay between the affective and cognitive subdivision of the ACC is unknown. From a theoretical perspective, several authors have suggested that the affective subdivision of the ACC may integrate salient affective and cognitive information (such as that derived from environmental stimuli or task demands), and subsequently modulate attentional processes within the cognitive subdivision accordingly (Mega et al. 1997, Mayberg 1997, Mayberg et al. 1999, Pizzagalli et al. 2001). In agreement with this hypothesis, dorsal anterior and posterior cingulate pathways devoted to attentional processes and amygdalar pathways devoted to affective processing converge within area 24 (Mega et al. 1997). These mechanisms may be especially important for understanding the repeatedly demonstrated finding that increased pretreatment activity in the rostral ACC is associated with eventual better treatment response (Mayberg et al. 1997; Ebert et al. 1991; Pizzagalli et al. 2001; Wu et al. 1992, 1999). In an influential paper, Mayberg and colleagues (1997) reported that unipolar depressed patients who responded to treatment after 6 weeks

showed higher pretreatment glucose metabolism in a rostral region of the ACC (BA 24a/b) compared with both nonresponders and nonpsychiatric comparison subjects. Recently, we (Pizzagalli et al. 2001) replicated this finding with EEG source localization techniques and demonstrated that even among those patients who respond to treatment, the magnitude of treatment response was predicted by baseline levels of activation in the same region of the ACC as identified by Mayberg et al. (1997). In addition, we suggested that hyperactivation of the rostral ACC in depression might reflect an increased sensitivity to affective conflict such that the disparity between one's current mood and the responses expected in a particular context activates this region of ACC, which then in turn issues a call for further processing to help resolve the conflict. This call for further processing is hypothesized to aid the treatment response.

One of the major outputs from the ACC is a projection to the PFC. This pathway may be the route via which the ACC issues a call to the PFC for further processing to address a conflict that has been detected. Abnormalities in PFC function in depression may thus arise as a consequence of the failure of the normal signals from ACC, or may be intrinsic to the PFC, or both. It is also possible and even likely that there are different subtypes of depression that may involve more primary dysfunction in different parts of the circuitry that we review in this chapter. We address this issue in more detail at the end of the chapter, but for now it is important to underscore the possibility that there may exist a primary ACC-based depression subtype and a primary PFC-based depression subtype. These subtypes might not conform to the phenomenological and descriptive nosologies that are currently prevalent in the psychiatric literature. The ACC-subtype may be reflected phenomenologically in a deficit in the "will-to-change," as such patients would not experience the conflict between their current state and the demands of everyday life. The PFC-subtype may fully experience such conflict and experience pronounced distress because the experience of the conflict between one's current state and the demands of everyday life are not sufficient to activate PFC-based mechanisms to organize and guide behavior toward the resolution of the conflict.

The findings reviewed above on PFC and ACC activation and morphological differences in depressed patients compared with controls underscore the considerable specificity within this region of the brain. There are important differences in connectivity between adjacent regions of cortical tissue, and future studies should examine patterns of functional connectivity in addition to activation differences that may distinguish between depressed patients and controls.

Hippocampus

FUNCTIONAL AND ANATOMICAL CONSIDERATIONS FOR UNDERSTANDING ITS ROLE IN AFFECT AND DEPRESSION   The hippocampus is critically involved in episodic, declarative, contextual, and spatial learning and memory (Squire & Knowlton

2000, Fanselow 2000). It is also involved in the regulation of adrenocorticotropic hormone secretion (Jacobson & Sapolsky 1991). With respect to conditioning, in recent years rodent studies have convincingly shown that the hippocampus plays a key role in the formation, storage, and consolidation of contextual fear conditioning (see Fanselow 2000 for review). In this form of hippocampal-dependent Pavlovian conditioning, fear (e.g., expressed in increased freezing) is acquired to places or contexts (e.g., a specific cage) previously associated with aversive events (e.g., shock). This fact has important implications for our understanding of the abnormalities in affective function that may arise as a consequence of hippocampal dysfunction.

In functional neuroimaging studies, hippocampal/parahippocampal activation has been reported during perception of several negatively valenced stimuli and/or experiencing of negatively valenced affective states, such as trace conditioning (Büchel et al. 1999), perception of aversive complex stimuli (Lane et al. 1997), threat-related words (Isenberg et al. 1999), increasing music dissonance (Blood et al. 1999), tinnitus-like aversive auditory stimulation (Mirz et al. 2000), vocal expressions of fear (Phillips et al. 1998), aversive taste (Zald et al. 1998), anticipatory anxiety (Javanmard et al. 1999), and procaine-induced affect (Ketter et al. 1996, Servan-Schreiber et al. 1998). However, it seems that valence is not the critical variable for evoking hippocampal activation. Indeed, hippocampal activation has been also reported during experimental manipulation of positive affect, such as re-evoking pleasant affective autobiographical memories (Fink et al. 1996), increases in winning in a game-like task (Zalla et al. 2000), and perception of a loved person (Bartels & Zeki 2000). Hippocampal activation was also correlated with long-term recognition memory for pleasant films (Hamann et al. 1999).

To reconcile these findings, we suggest that most of the experimental manipulations leading to hippocampal activation contain contextual cues. That is, we assume that they involve the consolidation of a memory for an integrated representation of a context similar to that associated with the presented stimulus (Fanselow 2000). This is clearly the case during Pavlovian and trace conditioning, for instance, but also during presentation of both positively and negatively valenced visual, olfactory, and auditory cues that may induce re-evocation and consolidation of contextual information associated with a similar situation in the past (see e.g., Nader et al. 2000).

Although in humans the mechanisms underlying contextual conditioning are still unclear, it is possible that plasticity in functional connectivity between the hippocampus and regions crucially involved in decoding the behavioral significance of incoming information, such as the amygdala and the pulvinar, may critically contribute to contextual learning (Morris et al. 1997, 1999), even when the information is presented below the level of conscious awareness (Morris et al. 1999). As recently reviewed by Davis & Whalen (2001), animal studies clearly suggest that the amygdala exerts a modulatory influence on hippocampal-dependent memory systems, possibly through direct projections from the basolateral nucleus of the amygdala. Consistent with this view, stimulation of the amygdala causes

long term potentiation (LTP) in the dentate gyrus of the hippocampus (Ikegaya et al. 1995a). Conversely, lesions to (Ikegaya et al. 1994) or local anesthetics within (Ikegaya et al. 1995b) the basolateral nucleus of the amygdala attenuate LTP in the dentate gyrus. Although extending conclusions from these rodent studies to humans is speculative at this stage, it is intriguing that most of the human neuroimaging studies reporting hippocampal activation during aversive affective manipulations also found amygdalar activation (Büchel et al. 1999, Isenberg et al. 1999, Ketter et al. 1996, Mirz et al. 2000, Servan-Schreiber et al. 1998, Zald et al. 1998). Future neuroimaging studies should directly test the interplay between the hippocampus and the amygdala in these processes and in fear-related learning and memory, especially in light of recent animal data suggesting an interaction between these regions for modulating extinction of conditioned fear (Corcoran & Maren 2001).

HIPPOCAMPUS AND DEPRESSION: THE FINDINGS   In their recent review, Davidson, and colleagues (Davidson et al. 2000a) noted that various forms of psychopathology involving disorders of affect could be characterized as disorders in context regulation of affect. That is, patients with mood and anxiety disorders often display normative affective responses but in inappropriate contexts. For example, fear that may be appropriate in response to an actual physical threat but persists following the removal of that threat, or sadness that may be appropriate in the acute period following a loss but persists for a year following that loss, are both examples of context-inappropriate emotional responding. In these examples the intensity and form of the emotion would be perfectly appropriate in response to the acute challenges, but when they occur in the absence of those acute stresses they can be viewed as context-inappropriate.

Given the preclinical and functional neuroimaging literature reviewed above, one may hypothesize that patients showing inappropriate context regulation of affect may be characterized by hippocampal dysfunction. Consistent with this conjecture, recent morphometric studies using MRI indeed reported smaller hippocampal volumes in patients with major depression (Sheline et al. 1996, 1999; Shah et al. 1998; Bremner et al. 2000; von Gunten et al. 2000; Steffens et al. 2000; Mervaala et al. 2000; but see Vakili et al. 2000, Ashtari et al. 1999), bipolar disorder (Noga et al. 2001), posttraumatic stress disorder (Bremner et al. 1995, 1997b, Stein et al. 1997), and borderline personality disorder (Driessen et al. 2000) (for review, see Sapolsky 2000, Sheline 2000). Where hippocampal volume reductions in depression have been found, the magnitude of reduction ranges from 8 to 19%. Recently, functional hippocampal abnormalities in major depression have also been reported at baseline using PET measures of glucose metabolism (Saxena et al. 2001). Whether hippocampal dysfunction precedes or follows onset of depressive symptomatology is still unknown.

In depression, inconsistencies across studies may be explained by several methodological considerations. First, as pointed out by Sheline (2000), studies reporting positive findings generally used MRI with higher spatial resolution

(∼0.5–2 mm) compared with those reporting negative findings (∼3–10 mm). Second, it seems that age, severity of depression, and most significantly, duration of recurrent depression may be important moderator variables. Indeed, studies reporting negative findings either studied younger cohorts [e.g., Vakili et al. (2000): 38 ± 10 years vs. Sheline et al. (1996): 69 ± 10 years; von Gunten et al. (2000): 58 ± 9 years; Steffens et al. (2000): 72 ± 8 years] or less severe and less chronic cohorts (Ashtari et al. 1999 vs. Sheline et al. 1996, Shah et al. 1998, Bremner et al. 2000). In a recent study (Rusch et al. 2002) we also failed to find hippocampal atrophy in a relatively young subject sample (33.2 ± 9.5 years) with moderate depression severity. Notably, in normal early adulthood (18–42 years), decreased bilateral hippocampal volume has been reported with increasing age in male but not female healthy subjects (Pruessner et al. 2001). Finally, in females initial evidence suggests that total lifetime duration of depression, rather than age is associated with hippocampal atrophy (Sheline et al. 1999), inviting the possibility that hippocampal atrophy may be a symptom rather than a cause of depression. Future studies should carefully assess the relative contribution of these possible modulatory variables in the hippocampal pathophysiology and examine hippocampal changes longitudinally in individuals at risk for mood disorders.

Structurally, the hippocampal changes may arise owing to neuronal loss through chronic hypercortisolemia, glial cell loss, stress-induced reduction in neurotrophic factors, or stress-induced reduction in neurogenesis, but the precise mechanisms are not completely known (Sheline 2000). In depression, the hypothesis of an association between sustained, stress-related elevations of cortisol and hippocampal damage has received considerable attention. This hypothesis is based on the observation that the pathophysiology of depression involves dysfunction in negative feedback of the hypothalamic-pituitary-adrenal axis (see Pariante & Miller 2001 for a review), which results in increased levels of cortisol during depressive episodes (e.g., Carroll et al. 1976). Higher levels of cortisol may, in turn, lead to neuronal damage in the hippocampus, because this region possesses high levels of glucocorticoid receptors (Reul & de Kloet 1986) and glucocorticoids are neurotoxic (Sapolsky et al. 1986). Because the hippocampus is involved in negative-feedback control of cortisol (Jacobson & Sapolsky 1991), hippocampal dysfunction may result in reduction of the inhibitory regulation of the hypothalamic-pituitary-adrenal axis, which could then lead to hypercortisolemia. Consistent with this view, chronic exposure to increased glucocorticoid concentrations has been shown to lower the threshold for hippocampal neuronal degeneration in animals (Gold et al. 1988, Sapolsky et al. 1990, McEwen 1998) and humans (Lupien et al. 1998). At least in nonhuman primates, this association is qualified by the observation that chronically elevated cortisol concentrations in the absence of chronic "psychosocial" stress do not produce hippocampal neuronal loss (Leverenz et al. 1999). Conversely, naturalistic, chronic psychosocial stress has been shown to induce structural changes in hippocampal neurons of subordinate animals (Magarinos et al. 1996). In depression, hippocampal volume loss has been shown to be associated with lifetime

duration of depression (Sheline et al. 1999), consistent with the assumption that long-term exposure to high cortisol levels may lead to hippocampal atrophy. However, this conjecture has not been empirically verified in humans.

Although intriguing, these findings cannot inform us about the causality between hippocampal dysfunction, elevated levels of cortisol, and most importantly, inappropriate context regulation of affect in depression. Unfortunately, none of the structural neuroimaging studies in depression investigating hippocampal volume were prospective and took into account cortisol data in an effort to unravel the causal link between cortisol output and hippocampal dysfunction.

The possibility of plasticity in the hippocampus deserves particular comment. In rodents, recent studies have shown hippocampal neurogenesis as a consequence of antidepressant pharmacological treatment (Chen et al. 2000, Malberg et al. 2000), electroconvulsive shock (Madhav et al. 2000), and most intriguingly, as a consequence of positive handling, learning, and exposure to an enriched environment (Kempermann et al. 1997; see Gould et al. 2000 for review). Neurogenesis in the adult human hippocampus has also been reported (Eriksson et al. 1998). Further, in patients with Cushing's disease, who are characterized by very high levels of cortisol, increases in hippocampal volume were significantly associated with the magnitude of cortisol decrease produced by microadrenomectomy (Starkman et al. 1999). As a corpus, these animal and human data clearly suggest that plasticity in the human hippocampus is possible (for reviews, see Duman et al. 2000, Jacobs et al. 2000, Gould et al. 2000), a finding that suggests that structural and functional changes in the hippocampus of depressed patients may be reversible.

In summary, preclinical and clinical studies converge in suggesting an association between major depression and hippocampal dysfunction. Future studies should (*a*) assess whether hippocampal atrophy precedes or follows increased onset of depression, (*b*) assess the causal relation between hypercortisolemia and hippocampal volume reduction, (*c*) directly test a putative link between inappropriate context-dependent affective responding and hippocampal atrophy, and (*d*) assess putative treatment-mediated plastic changes in the hippocampus.

Amygdala

FUNCTIONAL AND ANATOMICAL CONSIDERATIONS FOR UNDERSTANDING ITS ROLE IN AFFECT AND DEPRESSION   Although a link between amygdala activity and negative affect has been a prevalent view in the literature, particularly when examined in response to exteroceptive aversive stimuli (e.g., LeDoux 2000), recent findings from invasive animal studies and human lesion and functional neuroimaging studies are converging on a broader view that regards the amygdala's role in negative affect as a special case of its more general role in directing attention to affectively salient stimuli and issuing a call for further processing of stimuli that have major significance for the individual. Evidence is consistent with the argument that the amygdala is critical for recruiting and coordinating cortical arousal and vigilant attention for optimizing sensory and perceptual processing of stimuli associated

with underdetermined contingencies, such as novel, surprising, or ambiguous stimuli (see also Davis & Whalen 2001, Holland & Gallagher 1999, Whalen 1998). Most stimuli in this class may be conceptualized as having an aversive valence because we tend to have a negativity bias in the face of uncertainty (Taylor 1991).

AMYGDALA AND DEPRESSION: THE FINDINGS   In major depression, structural and functional abnormalities in the amygdala have been reported. Structurally, several recent studies reported an association between enlargement of amygdala volume and depression. This association has been found in depressed patients with bipolar disorders (Altshuler et al. 1998, Strakowski et al. 1999) as well as temporal lobe epilepsy (Tebartz van Elst et al. 1999, 2000). In a recent study Mervaala et al. (2000) observed significant asymmetry in amygdalar volumes (right smaller than left) in MDD patients but not the controls. In temporal lobe epilepsy patients with dysthymia, left amygdala volume was positively correlated with depression severity (Tebartz van Elst et al. 1999). Although these findings depict a relation between increased amygdalar volume and depression, it is important to stress that (*a*) the causal relations between the two entities are still unknown and (*b*) some inconsistencies among studies are present. Indeed, some studies reported either decreased bilateral volume in the amygdala core nuclei (Sheline et al. 1998) or null findings (Coffey et al. 1993, Pantel et al. 1997, Ashtari et al. 1999). Although the reasons are still unclear, it is interesting to note that two null findings were found in geriatric depression (Pantel et al. 1997, Ashtari et al. 1999).

Functionally, abnormal elevations of resting regional cerebral blood flow or glucose metabolism in the amygdala have been reported in depression during both wakefulness (Drevets et al. 1992) and sleep (Ho et al. 1996, Nofzinger et al. 1999). In a PET study Ho et al. (1996) reported increased absolute cerebral glucose metabolic in several brain regions, particularly the amygdala (+44%), in 10 unmedicated men with unipolar depression during non-rapid eye movement sleep. Further, in his recent review, Drevets (2001) reported data from five consecutive studies, in which increased regional cerebral blood flow or glucose metabolism has been consistently replicated in depressives with familial MDD or melancholic features. In a postmortem study, 5-HT2 receptor density was significantly increased in the amygdala of depressive patients committing suicide (Hrdina et al. 1993). Abnormally increased amygdalar activation has also been recently reported in bipolar depression (Ketter et al. 2001) and anxiety disorders, which often show a high degree of comorbidity with depression (Birbaumer et al. 1998; Liberzon et al. 1999; Rauch et al. 1996, 2000; Schneider et al. 1999; Semple et al. 2000; Shin et al. 1997).

Further establishing a link between depression and amygdalar activation, two studies have reported a positive correlation between amygdalar activation and depression severity or dispositional negative affect in patients with MDD (Drevets et al. 1992, Abercrombie et al. 1998). After pharmacologically induced remission from depression, amygdalar activation has been observed to decrease to normative values (Drevets 2001). In familial pure depressive disease, however, increased (left) amygdalar activation persists during the remitted phases (Drevets et al. 1992),

suggesting that at least in some subtypes of depression amygdalar dysfunction may be trait-like. Interestingly, remitted MDD patients showing symptom relapse as a consequence of serotonin depletion showed increased amygdalar activation prior to the depletion compared with those who do not relapse (Bremner et al. 1997a). Finally, in one of the first fMRI studies using an activation paradigm in depressed patients, Yurgelun-Todd et al. (2000) reported higher left amygdalar activation for bipolar patients than controls in response to fearful faces.

In light of the pivotal role of the amygdala in recruiting and coordinating vigilant behavior toward stimuli with underdetermined contingencies, hyperactivation of the amygdala in major depression may bias initial evaluation of and response to incoming information. Although still speculative, this mechanism may rely on norepinephrine, which (*a*) is oftentimes abnormally elevated in depression (e.g., Veith et al. 1994), (*b*) is involved in amygdala-mediated emotional learning (Ferry et al. 1999), and (*c*) is affected by glucocorticoid secretions, which are often elevated in MDD (e.g., Carroll et al. 1976). Thus, these findings may explain cognitive biases towards aversive or emotionally arousing information observed in depression.

Increased amygdalar activation in depression may also represent a possible biological substrate for anxiety, which is often comorbid with depression. In this respect, elevated levels of glucocortocoid hormones—which characterize at least some subgroups of patients with depression—may be especially relevant, since elevated glucocorticoid hormones have been shown to be associated with increased corticotropin-releasing hormone (CRH) in the amygdala. Increased CHR availability may increase anxiety, fear and expectation for adversity (Schulkin 1994).

In light of evidence suggesting a link between amygdalar activation, on one hand, and memory consolidation and acquisition of long-term declarative knowledge about emotionally salient information, on the other, the observations of dysfunctionally increased amygdalar activation in major depression are intriguing. As recently pointed out by Drevets (2001), tonically increased amygdalar activation during depressive episodes may favor the emergence of rumination based on increased availability of emotionally negative memories. Although still untested, it is possible that these aberrant processes may rely on dysfunctional interactions between the amygdala, the PFC, and the ACC. Notably, structural abnormalities have been reported in territories of the PFC intimately connected with the ACC (Drevets et al. 1997, Öngür et al. 1998b). ACC dysfunction, in particular, may lead to a decreased capability of monitoring potential conflict between memory-based ruminative processes and sensory information coming from the environment.

SUMMARY AND CONCLUSIONS

This chapter reviewed the circuitry that underlies the representation and regulation of emotion. It is this circuitry that exhibits different kinds of abnormalities in depression. Different territories of the PFC and ACC, the hippocampus, and the amygdala were considered. These structures are all interconnected in regionally

specific ways and exhibit bi-directional feedback. Abnormalities in the morphometry and functioning of each of these structures have been reported in depression. Because longitudinal studies that involve the measurement of brain structure and function in at-risk individuals have not yet been performed, we cannot specify which of the abnormalities may be primary in the sense of occurring first, and which may be secondary to dysfunctions initially occurring in another brain region. For example, PFC abnormalities may arise as a consequence of ACC abnormalities or may be independent. In addition, a paucity of work has examined functional and/or structural connectivity among these regions. Some of the abnormalities in depression may arise as a consequence of impaired connectivity, either functional, structural, or both. Future research should include measures of both functional (e.g., Cordes et al. 2000) and structural connectivity. The latter can be measured with diffusion tensor imaging (Le Bihan et al. 2001).

We have drawn upon the animal and human literature on basic processes in emotion and emotion regulation to help interpret the abnormalities that have been reported in depression and to highlight the kinds of studies that have not yet been performed but are important to conduct. The findings on the basic processes in animals and normal humans provide the foundation for a model of the major components in affect representation and regulation. The input to affect representation can be either a sensory stimulus or a memory. Most sensory stimuli are relayed through the thalamus and from there they can take a short route to the amygdala (LeDoux 2000) and/or go up to cortex. From both association cortex and from subcortical regions including the amygdala, information is relayed to different zones of the PFC. The PFC plays a crucial role in the representation of goals. In the presence of ambiguous situations, the PFC sends bias signals to other brain regions to facilitate the expression of task-appropriate responses in the face of competition with potentially stronger alternatives. We argued that in the affective domain the PFC implements affect-guided anticipatory processes. Left-sided PFC regions are particularly involved in approach-related appetitive goals, whereas right-sided PFC regions are involved in the maintenance of goals that require behavioral inhibition. Abnormalities in PFC function would be expected to compromise goal-instantiation in patients with depression. Left-sided hypoactivation would result in deficits in pre-goal attainment forms of positive affect, whereas right-sided hyperactivation would result in excessive behavioral inhibition and anticipatory anxiety. Hypoactivation in regions of the PFC with which the amygdala is interconnected may result in a decrease in the regulatory influence on the amygdala and a prolonged time course of amygdala activation in response to challenge. This might be expressed phenomenologically as perseveration of negative affect and rumination.

The ACC is critically involved in conflict monitoring and is activated whenever an individual is confronted with a challenge that involves conflict among two or more response options. According to an influential theory of ACC function (Carter et al. 1999), the ACC monitors the conflicts among brain regions. When such conflict is detected, the ACC issues a call for further processing to the PFC that then adjudicates among the various response options and guides behavior toward

a goal. The ACC is very frequently activated in neuroimaging studies of human emotion (see Bush et al. 2000 for review), in part because when emotion is elicited in the laboratory it produces response conflict. There is the general expectation to behave in an unemotional fashion because subjects are participating in a scientific experiment, yet there are the responses that are pulled by the emotional challenge, such as certain patterns of facial expression. This is commonly reported by subjects and is associated with ACC activation.

There is sometimes a conflict between an individual's mood state and the behavior that is expected of the individual in a particular social or role context. For example, among depressed individuals, their dispositional mood state may predispose them to set few goals and engage in little intentional action, yet the demands of their environments may include expectations to behave in specific ways. In an individual with normal levels of ACC activation, the signal from ACC would issue a call to other brain regions, the PFC being the most important, to resolve the conflict and engage in the appropriate goal-directed behavior. However, in an individual with abnormally low levels of ACC activation, the conflict between her dispositional mood state and the expectations of her context would not be effectively monitored and thus, the usual call for further processing would not be issued. The data on ACC function in depression most consistently reveal a pattern of decreased activation in certain regions of the ACC. Interestingly, those depressed patients with greater activation in the ventral ACC before antidepressant treatment are the ones most likely to show the largest treatment responses. In normal individuals, activation of the affective subdivision of the ACC may also be associated phenomonologically with the will to change.

The hippocampus appears to play an important role in encoding context. Lesions to the hippocampus in animals impair context conditioning. In addition, this structure has a high density of glucocorticoid receptors, and elevated levels of cortisol in animal models produce hippocampal cell death. In humans, various stress-related disorders, including depression, are associated with hippocampal volume reductions. Whether such hippocampal volume differences are a cause or a consequence of the depression cannot be answered from extant data. However, to the extent that hippocampal dysfunction is present, we would expect that such individuals would show abnormalities in the context-appropriate modulation of emotional behavior. This type of abnormality would be expressed as the display of normal emotion in inappropriate contexts. Thus, the persistence of sadness in situations that would ordinarily engender happiness could in part arise as a consequence of a hippocampally dependent problem in the context-modulation of emotional responses. We have shown such effects in rhesus monkeys (see Davidson et al. 2000a for review), but they have not yet been studied in depressed patients. The extensive connections between hippocampus and PFC would presumably provide the requisite anatomical substrate for conveying the contextual information to PFC to regulate emotional behavior in a context-appropriate fashion. The connections between hippocampus and PFC are another potential target of dysfunction in depression. It is possible that a certain subtype of individual exists wherein contextual

encoding is intact and PFC-implemented goal-directed behavior is intact, but context fails to adequately guide and reprioritize goals. In such cases, the functional and/or anatomical connectivity between hippocampus and PFC might be a prime candidate for dysfunction. The tools are now available to examine both types of connectivity using noninvasive measures.

The amygdala has long been viewed as a key site for both the perception of cues that signal threat and the production of behavioral and autonomic responses associated with aversive responding. As we have noted above, current evidence suggests that the amygdala's role in negative affect may be a special case of its more general role in directing attention and resources to affectively salient stimuli and issuing a call for further processing of stimuli that have potentially major significance for the individual. As with other parts of the circuit we have addressed, there are extensive connections between the amygdala and each of the other structures we have considered. The amygdala receives input from a wide range of cortical zones and has even more extensive projections back to cortex, enabling the biasing of cortical processing as a function of the early evaluation of a stimulus as affectively salient. Also like the other components of the circuit we have described, there are individual differences in amygdala activation both at baseline (Schaefer et al. 2000) and in response to challenge (see Davidson & Irwin 1999 for review). Moreover, it is likely that regions of the PFC play an important role in modulating activation in the amygdala and thus influencing the time course of amygdala-driven negative affective responding. In light of the associations that have been reported between individual differences in amygdala activation and affect measures, it is likely that when it occurs, hyperactivation of the amygdala in depression is associated more with the fear-like and anxiety components of the symptoms than with the sad mood and anhedonia. We have found that amygdala activation predicts dispositional negative affect in depressed patients but is unrelated to variations in positive affect (Abercrombie et al. 1998). Excessive activation of the amygdala in depressed patients may also be associated with hypervigilance, particularly toward threat-related cues, which further exacerbates some of the symptoms of depression.

There are several types of studies that need to be performed in light of the evidence reviewed in this chapter. Studies that relate specific abnormalities in particular brain regions to objective laboratory tasks that are neurally inspired and designed to capture the particular kinds of processing that are hypothesized to be implemented in those brain regions is needed. Relatively few studies of this kind have been conducted. Studies on depressed patients that examine relations between individual differences in neural activity and psychological phenomena almost always relate such neural variation to symptom measures that are either self-report or interview-based indices. In the future it will be important to complement the phenomenological description with laboratory measures that are explicitly designed to highlight the processes implemented in different parts of the circuit that we described.

Such future studies should include measures of both functional and structural connectivity to complement the activation measures. It is clear that interactions

among the various components of the circuitry we describe are likely to play a crucial role in determining behavioral output. Moreover, it is possible that connectional abnormalities may exist in the absence of abnormalities in specific structures.

Longitudinal studies of at-risk samples with the types of imaging measures that are featured in this review are crucial. We do not know if any of the abnormalities discussed above, both of a structural and functional variety, precede the onset of the disorder, co-occur with the onset of the disorder, or follow the expression of the disorder. It is likely that the timing of the abnormalities in relation to the clinical course of the disorder varies for different parts of the circuitry. The data reviewed earlier showing a relation between the number of cumulative days depressed over the course of the lifetime and hippocampal volume suggest that this abnormality may follow the expression of the disorder and represent a consequence rather than a primary cause of the disorder. However, before such a conclusion is accepted, it is important to conduct the requisite longitudinal studies to begin to disentangle these complex causal factors.

Finally, we regard the evidence presented in this review as offering very strong support for the view that depression refers to a heterogeneous group of disorders. It is possible that depression-spectrum disorders can be produced by abnormalities in many different parts of the circuitry reviewed. The specific subtype, symptom profile, and affective abnormalities should vary systematically with the location and nature of the abnormality. It is likely that some of the heterogeneity that might be produced by deficits in particular components of the circuitry reviewed will not map precisely onto the diagnostic categories we have inherited from descriptive psychiatry. A major challenge for the future will be to build a more neurobiologically plausible scheme for parsing the heterogeneity of depression based upon the location and nature of the abnormality in the featured circuitry. We believe that this ambitious effort will lead to considerably more consistent findings at the biological level and will also enable us to more rigorously characterize different endophenotypes that could then be exploited for genetic studies.

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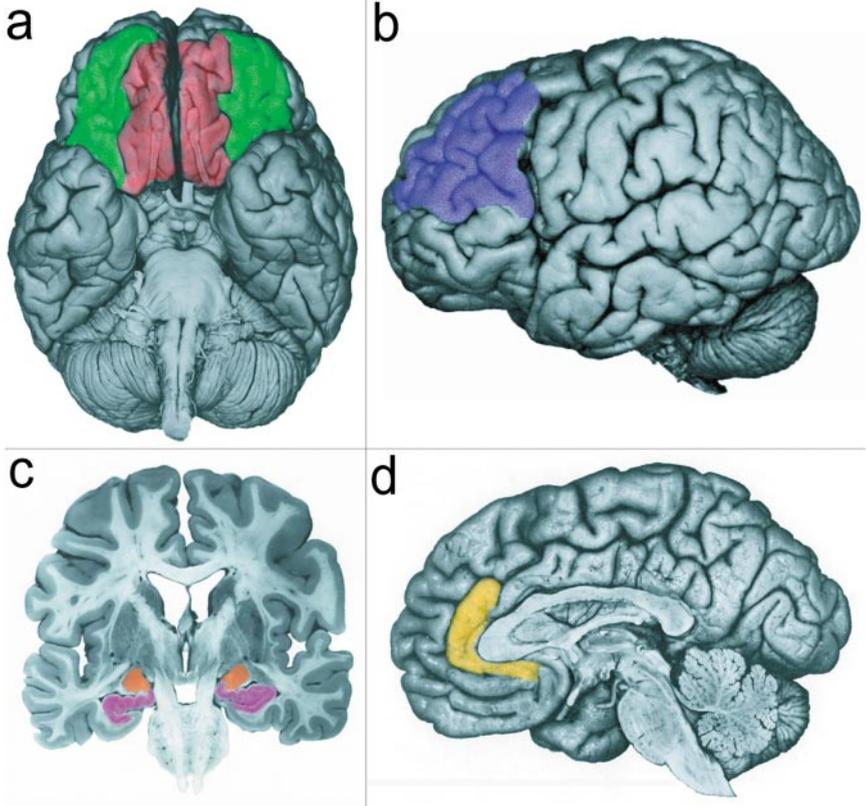
Figure 1 Key brain regions involved in affect and mood disorders. (*a*) Orbital prefrontal cortex (*green*) and the ventromedial prefrontal cortex (*red*). (*b*) Dorsolateral prefrontal cortex (*blue*). (*c*) Hippocampus (*purple*) and amygdala (*orange*). (*d*) Anterior cingulate cortex (*yellow*).
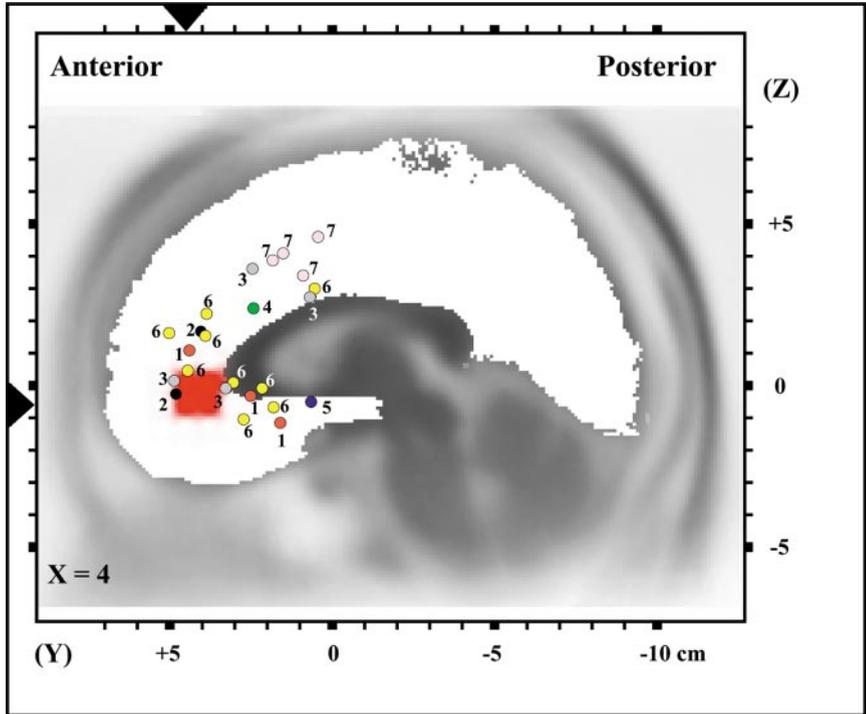
Figure 2 Summary of functional brain imaging studies of anterior cingulate cortex (ACC) involvement in depression as well as during various cognitive and affective task manipulations. Foci of ACC activation or deactivation were registered to a common stereotaxic brain atlas (Talairach & Tournoux 1988) and plotted on a sagittal brain slice (anterior part of the head to the left). The large red area and the black triangles show the location of the ACC cluster found to be associated with degree of treatment response in our previous EEG study (Pizzagalli et al. 2001). The studies of depressed subjects showed pretreatment hyperactivity among patients who responded to treatment (1); posttreatment decreased activity in responders (2); hypoactivity in depressed subjects (3); increased activity with remission of depression (4); and decreased activity with remission of depression (5). Studies involving emotional (6) and cognitive (7) tasks in nonpsychiatric subjects are also reported. Coordinates in mm (Talairach & Tournoux 1988), origin at anterior commissure; (X) = left (−) to right (+); (Y) = posterior (−) to anterior (+); (Z) = inferior (−) to superior (+). Adapted from Pizzagalli et al. (2001).