CHAPTER 10

Representation and Regulation of Emotion in Depression

Perspectives from Affective Neuroscience

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Affective neuroscience is the subdiscipline 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 is based on a 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 chasm between the literatures that focus on normal emotion and on the disorders of emotion. Historically, because these research traditions have had little to do with one another, they have emerged independently. However, affective neuroscience has helped to integrate these approaches into a more unified project that focuses on understanding individual differences in affective style, their constituent components, and the neural bases (see, e.g., Davidson, 2000; Davidson, Jackson, & Kalin, 2000). This chapter is an update of our Chapter 9 in the first edition of this *Handbook* and emphasizes findings published in the past 3 years.

Affective neuroscience takes as its overall aims a similar project to that pursued by its cognate discipline, cognitive neuroscience, though it focuses 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 (see Joormann, Chapter 13, this volume). Instead, contemporary cognitive scientists and neuroscientists have developed laboratory tasks to interrogate subjects and reveal more elementary cognitive function.

These more elementary processes can then be examined using imaging methods in humans, lesion methods in animals, and the study of human patients with focal brain damage. Affective neuroscience uses the same strategy to approach emotion. Global constructs of emotion are giving way to more specific and elementary constituents that can be examined with objective laboratory measures. For example, Davidson's laboratory has been developing methods to probe the chronometry of affect using both neuroimaging and peripheral startle measures. These measures allow us to examine an anticipatory period prior to the delivery of an emotional stimulus, a recovery period following the delivery of an emotional stimulus, and other, related parameters that can be assessed objectively and that reveal systematic individual differences (see Davidson, 1998, 2000; Jackson et al., 2003). Though it is still tempting and often important to obtain measures of subjects' conscious experience of the contents of their emotional states and traits, these self-reports no longer comprise the sole source of information about emotion.

Because there are recent basic literature reviews on the circuitry underlying emotion and emotion regulation (e.g., Davidson & Irwin, 1999; Davidson, Jackson, & Kalin, 2000; Davidson, Putnam, & Larson, 2000; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Ochsner & Gross, 2005; Rolls, 1999), we do not review these data systematically in this chapter. We wish to underscore at the outset that one of crucial issues that plagues research in this area is the heterogeneity of depression (see Ingram & Siegle, Chapter 4, this volume). From an examination of the inconsistencies across studies, it is apparent that traditional methods for parsing heterogeneity based on 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 are provided throughout this chapter.

We have three broad goals:

1. To review the functional role of the prefrontal cortices, anterior cingulate, hippocampus, and amygdala in affect and emotion regulation (see Figure 10.1 for an illustration of these structures and their locations).
2. To review the functional and structural abnormalities that have been found in these regions relative to depression.
3. Based on the first and second goals (a) to advance hypotheses about symptom clusters that may arise as a consequence of dysfunctions in specific regions; and (b) to offer suggestions for different ways of parsing the heterogeneity of depression to reflect more directly the circuitry of emotion and emotion regulation in the brain.

THE EMOTIONAL CIRCUITRY OF THE BRAIN AND ITS DYSFUNCTION IN DEPRESSION

Prefrontal Cortex

The Role of the Prefrontal Cortex in Emotion and Emotion Regulation

Abnormalities in activation of prefrontal regions in depression have been reported more frequently than those for any other brain region, mostly in the direction of decreased bilateral or predominantly left-sided activation (Davidson, Abercrombie, Nitschke, & Putnam, 1999; George, Ketter, & Post, 1994). Miller and Cohen (2001) outlined a comprehensive theory of

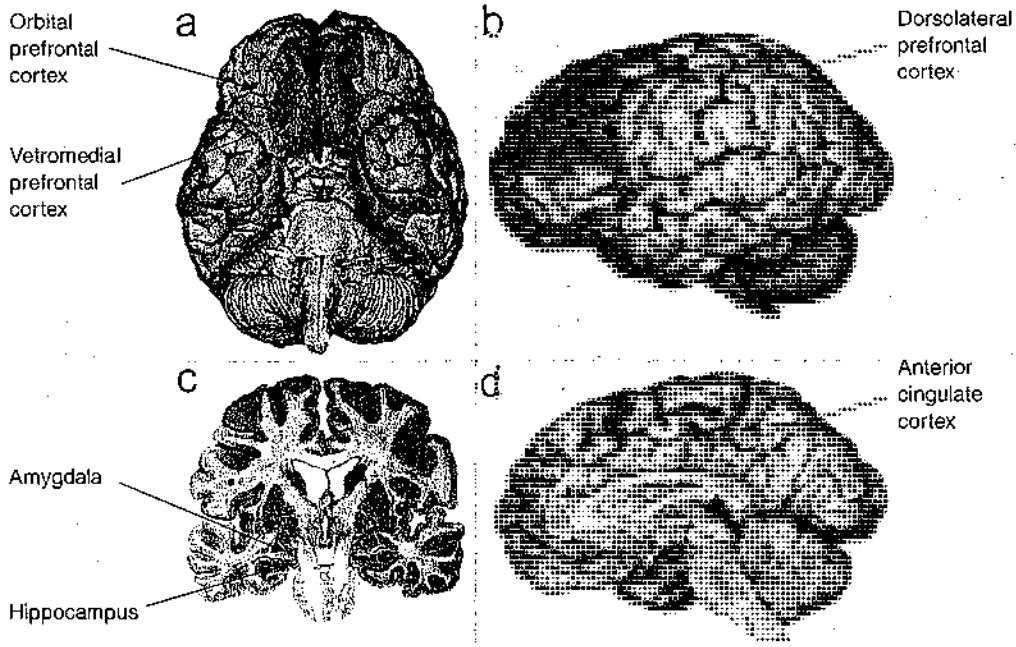

FIGURE 10.1. Key brain regions involved in affect and mood disorders: (a) orbital prefrontal cortex and ventromedial prefrontal cortex; (b) dorsolateral prefrontal cortex; (c) hippocampus and amygdala; and (d) anterior cingulate cortex.

prefrontal function based on nonhuman 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 offers a potent response alternative that may not be in the best service of the overall goals of the person. In such a case, the PFC is required to generate 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). The instantiation of 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.

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, Jackson, & Kalin, 2000). 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, re-

quires left-sided PFC activation. In contrast, right-sided PFC regions 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 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 on those trials in which a cue to inhibit the response is presented. Several 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 signaling response inhibition, presented in the context of other stimuli toward which a strong approach set was established (Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Garavan, Ross, & Stein, 1999; Konishi et al., 1999; see Dillon & Pizzagalli, 2007, for recent review).

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

Results from recent neuroimaging and electrophysiological studies suggest that the orbital cortex, and the ventral frontal cortex in particular, is especially important for the representation of rewards and punishments, and that different sectors within this cortex may emphasize reward versus punishment (Kawasaki et al., 2001; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). More specifically, a left-sided medial region of the orbitofrontal cortex (OFC) appears particularly responsive to rewards, whereas a lateral right-sided region appears particularly responsive to punishments (O'Doherty et al., 2001). Differential behavioral responsivity to reward versus punishment has been found in two studies in our laboratory (Henriques & Davidson, 2000; Henriques, Glowacki, & Davidson, 1994). In particular, whereas normal individuals exhibited systematic modificarion of response bias to monetary reward, depressed patients failed to show such changes, but they did show response bias shifts in response to monetary punishment. Pizzagalli, Jahn, and O'Shea (2005) have more recently replicated and extended this finding, and demonstrated that individuals with elevated levels of depressive symptoms fail to show a response bias to reward. The precise neural correlates of individual differences in response bias to reward remain to be fully characterized.

PFC in Depression

Consistent with prior literature, recent reports have documented decreased activation in both dorsolateral and dorsomedial PFC, as well as the pregenual region of the anterior cingulate gyrus in depressed patients (see Drevets [1998] for a review of the early studies and Fitzgerald, Laird, Maller, & Daskalakis [2008] for a more recent review of this literature). 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 MRI-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 and colleagues (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) regions and also in the amygdala (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). 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: whereas some studies have found increases in these regions (Kennedy et al., 2001), others have reported decreases (e.g., Brody et al., 1999; Mayberg et al., 1999). In more recent work, investigators have developed behavioral paradigms hypothesized to differentiate more sensitively between depressed patients and controls. For example, we (Schaefer, Putnam, Benca, & Davidson, 2006) presented positive social stimuli in several different categories to depressed patients and controls on two occasions—the first prior to treatment when patients were in episode, and the second following approximately 22 weeks of treatment with venlaxfaxine. We found that at the initial testing occasion, when patients were in a depressive episode, there was hypoactivation in a circuit that included several regions of PFC, including medial, inferior, and superior frontal gyri. Similar results that also included a blunted ventral striatal response to positive stimuli have been reported by others (e.g., Epstein et al., 2006). Fu et al. (2007) reported a similar hypoactivated response to happy facial expressions.

As suggested earlier, recent reports of anatomical PFC differences between depressed patients and normal controls are of critical import to any claims made about functional differences between these two groups of individuals. Consistent with earlier work by Coffey and colleagues (1993), who found that depressed inpatients had 7% smaller frontal lobe volumes than those of nonpsychiatric controls, Drevets and colleagues (1997) reported that patients with unipolar and bipolar depression with a family history of mood disorders showed 48 and 39% reductions in subgenual PFC volume, respectively. In a postmortem study by the same group (Öngür, An, & Price, 1998), glial cell number was significantly reduced in subgenual PFC in both unipolar (24%) and bipolar patients (41%) with family history of major depressive disorder (MDD). No significant effects were observed for nonfamilial MDD or bipolar disorder (BD). Rajkowska (2000) has further examined alterations in neuronal and glial histopathology in postmortem brains of patients with mood disorders. She and her colleagues found that left prefrontal cortices (no other brain areas were examined) of subjects with MDD 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, 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 and colleagues do 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 dis-

cordant for mood disorders to ascertain whether the anatomical abnormalities are found in the affected twin only (see Levinson, Chapter 8, this volume).

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, Schwartz, Hardin, Baldwin, & Kline, 1998, Bruder et al., 1997; Debener et al., 2000; Gotlib, Ranganath, & Rosenfeld, 1998; Pauli, Wiedemann, & Nickola, 1999; but see Reid, Duke, & Allen [1998] for complications, Davidson [1998] for a rejoinder, and Davidson [2004] for a more recent review).

In an important extension of the work on electrophysiological asymmetries, Bruder and his colleagues (2001) examined whether brain electrical asymmetry measnres acquired during a pretreatment period predicted response to selective serotonin reuptake inhibitor (SSRI) treatment. They found that, among women in particular, 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 on 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

The Role of the Anterior Cingulate Cortex in Emotion and Emotion Regulation

Several theorists have proposed that the anterior cingulate cortex (ACC) acts as a bridge between attention and emotion (Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995; Ebert & Ebmeier, 1996; Mayberg et al., 1997; Vogt, Nimchinsky, Vogt, & Hof, 1995). In their review, Thayer and 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 behaviors have been described (Devinsky et al., 1995; Vogt, Finch, & Olson, 1992). However, to fully understand the role of the ACC in psychopathology, affective states, and emotional processing, it seems mandatory 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 [BAs] 25, 32, 33, and rostral BA 24). The second, referred to as the *cognitive subdivision*, involves dorsal regions of the ACC (caudal BAs 24′ and 32′, cingulate motor area; see Bush et al., 2000). The affect subdivision possesses extensive connections with limbic and paralimbic regions, such as the amygdala, nucleus accumbens, OFC, periaqueductal gray, 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. Because of its strong connections with the lateral hypothalamus, the subgenual ACC (BA 25) is considered the most important autonomic region within the frontal region (Öngür et al., 1998).

Conversely, the cognitive subdivision is intimately connected with 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, some evidence points to a functional differentiation between ventral (affective) and dorsal (cognitive) ACC subdivisions (Bush et al., 1998, 2000; Whalen, Bush, et al., 1998) though other evidence, particularly from the pain literature, challenges this simple differentiation (Salomons, Johnstone, Backonja, & Davidson, 2004).

From a functional perspective, activation of the dorsal region of the ACC has been reported during interference between competing information sources (Pardo, Pardo, Janer, & Raichle, 1990), visual attention (Nobre et al., 1997), monitoring of cognitive (Carter et al., 2000; MacDonald, Cohen, Stenger, & Carter, 2000) and reward-related (Rogers et al., 1999) conflicts, task difficulty (Paus et al., 1997), and increased risk-associated outcome uncertainty (Critchley, Mathias, & Dolan, 2001), among other experimental manipulations. A common denominator among these experimental conditions is that they all required modulation of attention or executive functions and monitoring of competition (Bush et al., 2000). The role of the ACC in conflict monitoring has been especially emphasized by Cohen and colleagues (Carter, Botvinick, & Cohen, 1999; Carter et al., 2000; Miller & Cohen, 2001), who 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 or interfere with each other. According to the *competition monitoring hypothesis*, the cognitive subdivision of the ACC monitors conflicts or cross-talk 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 (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. From a functional perspective, activation of the ventral ACC has been reported during various emotional states and manipulations (for reviews, see Bush et al., 2000; Reiman, 1997). Collectively, recent findings suggest that the ventral ACC is critically involved in conscious experience of affect, and possibly of uncertainty, conflict, and expectancy violation arising from affectively and motivationally salient situations (see below).

In light of the many types of experimental manipulations that activate the ACC, is there a common denominator underlying activation of the rostral–ventral ACC in such disparate experimental conditions, such as pain, classical conditioning, transient mood, activation of primary drive states, Stroop task, and perceiving facial expressions, among others? A possible answer to this question is that the ventral 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 ventral 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. Extant 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, including most laboratory situations (Bush et al., 2000; Ochsner & Barrett, 2001). Relatedly, 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 (OCD) (Breiter, Rauch, et al., 1996; Rauch,

Savage, Alpert, Fischman, & Jenike, 1997), simple phobia (Rauch et al., 1995), and posttraumatic stress disorder (PTSD) (Rauch et al., 1996; Shin et al., 1997), in which conflicts between response tendencies and environments are prominent. Interestingly, psychosurgical lesions of the ACC has been used as a treatment for mood and anxiety disorders (e.g., Baer et al., 1995; see Binder & Iskandar [2000] for a review), possibly because of a reduction of conflict monitoring and uncertainty that otherwise characterize these psychiatric conditions.

ACC in Depression

In major depression, decreased ACC activation relative to controls has been reported repeatedly. In single-photon emission computed tomography (SPECT) studies, decreased regional cerebral blood flow (rCBF) in the left (Curran, Tucker, Kutas, & Posner, 1993; Mayberg, Lewis, Regenold, & Wagner, 1994) or right (Ito et al., 1996) ACC has been found in medicated patients with unipolar depression compared to controls. Decreased ACC activation has been recently replicated with 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, the region of the ACC found to be hypoactive in major depression (dorsal ACC: dorsal region of BA 32; BAs 24′ and 32′) appears to be different from the region found to be hyperactive in eventual treatment responders (ventral and rostral ACC, including pregenual BAs 24 and 32). Whereas the state of being depressed is associated with reduced dorsal ACC activity (previously discussed), remission has been characterized by increased activity in the same region (Bench, Frackowiak, & Dolan, 1995; Buchsbaum et al., 1997; Mayberg et al., 1999). Based on the functional neuroimaging and animal literature reviewed earlier, it is conceivable to postulate that (1) hypoactivation in dorsal regions of the ACC (BAs 24′ and 32′) may be associated with impaired modulation of attention or executive functions and impaired monitoring of competition among various response options; (2) hypoactivation in ventral regions of the ACC (BAs 24 and 32) may be associated with blunted conscious experience of affect, hypoarousal, anhedonia, and reduced coping potential in situations characterized by uncertainty, conflict, and expectancy violation between the environment and one's affective state; and (3) hyperactivation in ventral regions of the ACC may be associated with increased attentional and behavioral responses to anxiety-provoking situations, especially in subjects with depression and comorbid anxiety. Such hyperactivation may cause attentional and affective stereotypies. Although future studies will be needed to test these assumptions more explicitly, recent findings are consistent with some of them. For example, in a fluorodeoxyglucose–positron emission tomography (FDG-PET) study, Brody and colleagues (2001) found that reduction of anxiety/somatization symptoms was associated with decreased activation in the ventral ACC. Conversely, improvement in psychomotor retardation symptoms was associated with increased activation in the dorsal ACC. In a combined EEG-PET study using source localization, we observed that melancholic depressed subjects showed evidence of hypoactivation in BA 25 compared to both nonmelancholic depressed and control subjects (Pizzagalli et al., 2004).

Several recent studies have examined differences between depressed and control subjects on cognitive and affective tasks hypothesized to be mediated by the ACC, along with either simultaneous recordings of ACC function or examination of baseline ACC function. In one of our studies, we administered the Eriksen flanker task to subjects whose levels of depressive symptoms differed (Pizzagalli, Peccoralo, Davidson, & Cohen, 2006). We found that subjects high in depressive symptoms showed significantly lower accuracy after incor-

rect versus correct trials. Moreover, using source localized high-density EEG recordings, we observed that these high depression subjects had significantly reduced baseline gamma activity (36–44 Hz) within the ventral but not the dorsal ACC. Extending these findings to a clinical sample, Holmes and Pizzagalli (2008) recently reported that unmedicated subjects with major depression were characterized by impaired performance in trials immediately following a mistake. Interestingly, subjects with depression showed hyperactivation in the rostral ACC 80 ms after committing an error. Moreover, unlike control subjects, patients failed to recruit DLPFC regions 472 ms after error commission. Based on these and related findings (e.g., Alexopoulos et al., 2007; Chiu & Deldin, 2007), Holmes and Pizzagalli concluded that behavioral impairments were associated with exaggerated automatic detection of unfavorable performance outcomes and inability to recruit cognitive control after error commission. In an important recent study using fMRI, Steele, Kumar, and Ebmeier (2007) investigated the response to feedback in patients with depression and healthy controls. They found that controls responded to negative feedback with an increase in reaction time and activation of the dorsal ACC. Patients with depression showed neither a change in reaction time following negative feedback nor an alteration of the signal in ACC. Knutson, Bhanji, Cooney, Atlas, and Gotlib (2007) examined the anticipation of monetary gain or loss in healthy controls and in patients with depression. They found accentuated activation of the ACC during anticipation of increasing gains, suggestive of increased conflict during the anticipation of gains.

As noted, early on Drevets and colleagues (1997) reported an anatomical difference in the pregenual region of the ACC, with depressed patients showing smaller gray matter volume in this region. Several more recent studies have also reported volume reductions in this and bordering areas of the ACC (Caetano et al., 2006; Coryell, Nopoulos, Drevets, Wilson, & Andreasen, 2005; Tang et al., 2007).

The interplay between the affective and cognitive subdivisions of the ACC is currently unknown. From a theoretical perspective, several authors have suggested that the affective subdivision of the ACC may integrate salient affective and cognitive information (e.g., that derived from environmental stimuli or task demands), and subsequently modulate attentional processes within the cognitive subdivision accordingly (Mayberg et al., 1997, 1999; Mega, Cummings, Salloway, & Malloy, 1997; Pizzagalli, Pascual-Marqui, 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 BA 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 (Chen et al., 2007; Ebert, Feistel, & Barocka, 1991; Mayberg et al., 1997; Pizzagalli, Pascual-Marqui, et al., 2001; Wu et al., 1992, 1999). In an influential article, Mayberg and colleagues (1997) reported that patients with unipolar depression who responded to treatment after 6 weeks showed higher pretreatment glucose metabolism in a rostral region of the ACC (BA 24a/b) compared to both nonresponders and nonpsychiatric comparison subjects. We (Pizzagalli, Pascual-Marqui, 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 that identified by Mayberg and colleagues. 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 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 PFC. This pathway may be the route through which the ACC issues a call to the PFC for further processing to address a conflict that has been detected. Thus, abnormalities in PFC function in depression may arise as a consequence of the failure of the normal signals from the ACC, may be intrinsic to the PFC, or both. Findings of disrupted functional connectivity within frontocingulate pathways during both resting (Pizzagalli, Oakes, & Davidson, 2003) and task-induced (Holmes & Pizzagalli, 2008) states in subjects with depression is consistent with the hypothesis that dysfunctional interaction between ACC and PFC regions might play an important role in the pathophysiology of depression. It is also possible, and even likely, that different subtypes of depression may involve primary dysfunction in one or another part of the circuitry that we review in this chapter. We address this issue in more detail at the end of the chapter; 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 currently prevalent phenomenological and descriptive nosologies in the psychiatric literature.

Hippocampus

The Role of the Hippocampus in Emotion and Emotion Regulation

The hippocampus is critically involved in episodic, declarative, contextual, and spatial learning and memory (Fanselow, 2000; Squire & Knowlton, 2000). In addition, the hippocampus is also importantly involved in the regulation of adrenocorticotropic hormone (ACTH) secretion (Jacobson & Sapolsky, 1991). With respect to conditioning, rodent studies have convincingly shown that the hippocampus plays a key role in the formation, storage, and consolidation of contextual fear conditioning (for a review, see Fanselow, 2000), in part through its interaction with the amygdala (Maren & Hobin, 2007). 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 the experience of negatively valenced affective states, snch as trace conditioning (Büchel, Dolan, Armony, & Friston, 1999), perception of aversive complex stimuli (Lane, Fink, Chau, & Dolan, 1997), threat-related words (Isenberg et al., 1999), increasing music dissonance (Blood, Zatorre, Bermudez, & Evans, 1999), tinnitus-like aversive auditory stimulation (Mirz, Gjedde, Sodkilde-Jrgensen, & Pedersen, 2000), vocal expressions of fear (Phillips, Yonng, et al., 1998), aversive taste (Zald, Lee, Fluegel, & Pardo, 1998), anticipatory anxiety (Javanmard et al., 1999), procaine-induced affect (Ketter et al., 1996), and monetary penalties (Elliott & Dolan, 1999). 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 reevoking pleasant affective autobiographical memories (Fink et al., 1996), increases in winning in a game-like task (Zalla et al., 2000), and perception of the loved person (Bartels & Zeki, 2000). Also, hippocampal acti-

vation has been found to be correlated with long-term recognition memory for pleasant films (Hamann, Ely, Grafton, & Kilts, 1999).

In reconciling these findings, we suggest that most of the experimental manipulations leading to hippocampal activation contain contextual cues (see Davidson, Jackson, & Kalin, 2000); 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 not only Pavlovian and trace conditioning, for instance, but also presentation of both positively and negatively valenced visual, olfactory, and auditory cues that may induce reevocation and consolidation of contextual information associated with similar situation in the past (e.g., Nader, Schafe, & LeDoux, 2000). Although the mechanisms underlying contextual conditioning in humans 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, Friston, & Dolan, 1997; Morris, Ohman, & Dolan, 1999), even when the information is presented below the level of conscious awareness (Morris et al., 1999). As reviewed by Davis and 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) induction in the dentate gyrus of the hippocampus (Ikegaya, Abe, Saito, & Nishiyama, 1995). Conversely, lesions to (Ikegaya, Saito, & Abe, 1994) or local anesthetics within (Ikegaya, Saito, & Abe, 1995) the basolateral nucleus of the amygdala attenuate LTP in the dentate gyrus. Although drawing conclusions from these rodent studies to humans is speculative at this stage, it is intriguing that most of the human neuroimaging studies that report hippocampal activation during aversive affective manipulations have also found amygdalar activation (Büchel et al., 1999; Dougal, Phelps, & Davachi, 2007; Isenberg et al., 1999; Ketter et al., 1996; Mirz et al., 2000; Zald et al., 1998). Future neuroimaging studies should test directly 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 interplay between these regions in modulating extinction of conditioned fear (Corcoran & Maren, 2001).

Hippocampus in Depression

In their review, Davidson, Jackson, and Kalin (2000) noted that various form of psychopathology involving disorders of affect may 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. Given the preclinical and functional neuroimaging literature reviewed earlier, 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 hippocampal atrophy in patients with major depression (Bremner et al., 2000; Colla et al., 2007; Lange & Irle, 2004; Maller, Daskalakis, & Fitzgerald, 2007; Mervaala et al., 2000; Neumeister et al., 2005; Shah, Ebmeier, Glabus, & Goodwin, 1998; Sheline, Sanghavi, Mintun, & Gado, 1999; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Steffens et al., 2000; von Gunten, Fox, Cipolotti, & Ron, 2000; but see Ashtari et al., 1999; Vakili et al., 2000), BD (Noga, Vladar, & Torrey, 2001), PTSD (Bremner et al., 1995; Bremner, Innis, et al., 1997; Stein, Koverola, Hanna, Torchia, & McClarty, 1997), and borderline personality disorder

(Driessen et al., 2000; for reviews, see Sapolsky, 2000; Sheline, 2000). Where hippocampal volume reductions in depression have been found, the magnitude of reduction ranges from 8 to 19%. Functional hippocampal abnormalities in major depression have been also reported at baseline by researchers using PET measures of glucose metabolism (e.g., 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 (~0.5–2.0 mm) compared to 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, researchers 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. Bremner et al., 2000; Shah et al., 1998; Sheline et al., 1996). In a study from our laboratory (Rusch, Abercrombie, Oakes, Schaefer, & Davidson, 2001), we also failed to find hippocampal atrophy in a relatively young subject sample (33.2 ± 9.5 years) with moderate depression severity. In a study of pediatric depression, Rosso and colleagues (2005) found no hippocampal volume difference between groups. 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, Collins, Pruessner, & Evans, 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. Other recent evidence suggests that the extent of hippocampal atrophy in depression may interact with specific genetic factors. For example, Frodl and colleagues (2007) found that both depressed patients and controls carrying the Met allele for brain-derived neutropic factor (BDNF) gene had significantly smaller hippocampal volumes than did comparison subjects homozygous for the Val-BDNF allele. In addition, Frodl and colleagues found that depressed patients as a group had significantly smaller hippocampal volumes than did controls. Taylor and colleagues (2005) observed a complex interaction between age of onset of depression and polymorphisms in the promoter region of the serotonin transporter gene on hippocampal volume. In the patients with early onset, those patients homozygous for the short allele (S/S genotype) had smaller hippocampal volumes than did comparison patients. In an important, recent study on monogygotic twins, de Geus and colleagues (2007) marshal evidence to show that volume reductions in the hippocampus are present only in the co-twin at risk for depression and anxiety compared to his or her identical co-twin. These findings convincingly demonstrate at least some important environmental etiology for the hippocampal volume reduction found in depression.

Structurally, the hippocampal changes may arise due 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 (HPA) axis (see Pariante & Miller [2001] for a review), which results in increased levels of cortisol during depressive episodes (e.g., Carroll, Curtis, & Mendels, 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, Krey, & McEwen, 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 HPA 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, Goodwin, & Chrousos, 1988; McEwen, 1998; Sapolsky, Uno, Rebert, & Finch, 1990) 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, McEwen, Flugge, & Fuchs, 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 verified empirically in humans.

Although intriguing, these findings cannot inform us about the causality among hippocampal dysfunction, elevated levels of cortisol, and most importantly, inappropriate context regulation of affect in depression. In one of the few studies that examined associations between hippocampal volume and basal cortisol, Colla and colleagues (2007) found no relation between the variables. It may be that with a denser cortisol sampling protocol that includes assessment of dirurnal slope, such relations might be uncovered. Unfortunately, none of the structural neuroimaging studies of depression that investigated 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. Studies of rodents have shown hippocampal neurogenesis as a consequence of antidepressant pharmacological treatment (Chen, Rajkowska, Du, Seraji-Bosorgzad, & Manji, 2000; Malberg, Eisch, Nestler, & Duman, 2000), electroconvulsive shock (Madhav, Pei, Grahame-Smith, & Zetterstrom, 2000) and, most intriguingly, as a consequence of positive handling, learning, and exposure to an enriched euvironment (Kempermann, Kuhn, & Gage, 1997; for a review, see Gould, Tanapat, Rydel, & Hastings, 2000). In humans, neurogenesis in the adult human hippocampus has been also reported (Eriksson et al., 1998). Furthermore, in patients with Cushing's disease, who are characterized by very high levels of cortisol, increases in hippocampal volume were significantly associated with 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, Malberg, Nakagawa, & D'Sa, 2000; Gould et al., 2000; Jacobs, Praag, & Gage, 2000), which suggests that structural and functional changes in the hippocampus of a depressed patient may be reversible. Indeed, recent formulations underscore the possible role of underlying hippocampal neurogenesis in some of the behavioral effects of antidepressant treatment (Sahay & Hen, 2007).

In summary, preclinical and clinical studies converge in suggestiug an association between major depression and hippocampal dysfunction. Future studies should (1) assess whether hippocampal atrophy precedes or follows increased onset of depression; (2) assess the causal relation between hypercortisolemia and hippocampal volume reduction; (3) directly test a putative link between inappropriate, context-dependent affective responding

and hippocampal atrophy; and (4) assess putative treatment-mediated plastic changes in the hippocampus.

Amygdala

The Role of the Amygdala in Emotion and Emotion Regulation

Although a link between amygdalar 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, human lesion, and functional neuroimaging studies are converging on a broader view that regards the role of the amygdala 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. Extant 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 (e.g., 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).

The amygdala and the structures with which it is interconnected, particularly regions of the PFC, play a crucial role in the regulation of emotion (for a review, see Ochsner & Gross, 2005). Recently, Urry and colleagues (2006) demonstrated that voluntary regulation of emotion using cognitive reappraisal is associated with systematic changes in activation of the amygdala in normal subjects. Specifically, the down-regulation of emotion is associated with decreased activation in the amygdala compared with an attend control condition. In addition, in this study, we examined which brain regions were activated when the amygdala was down-regulated and found that the ventromedial prefrontal cortex (vmPFC) was strongly reciprocally related to the amygdala (correlations > .8). During the down-regulation of emotion, the vmPFC was activated. Moreover, in this study we demonstrated that those subjects with the greatest decrease in amygdala activation and the greatest increase in vmPFC activation during the down-regulation of emotion had the steepest slope of diurnal variation in basal cortisol. These individuals may be thought of as the good emotion regulators, and they especially showed low levels of evening cortisol (correlations in the range of .7).

The Role of the Amygdala in Depression

In major depression, structural and functional abnormalities in the amygdala have been reported. Relative to structure, several studies have reported an association between increased amygdalar volume and depression. This association has been found in depressed patients with bipolar disorders (Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; Strakowski et al., 1999) as well as temporal lobe epilepsy (TLE; Tebartz van Elst, Woermann, Lemieux, & Trimble, 1999, 2000). Mervaala and colleagues (2000) observed significant asymmetry in amygdalar volumes (right smaller than left) in patients with MDD but not in controls. In patients with TLE and dysthymia, left amygdalar volume was positively correlated with depression severity, as assessed with the Beck Depression Inventory (BDI) (Tebartz van Elst et al., 1999). More recently, Munn and colleagues (2007) failed to find significant differences in amygdalar volume between depressed and control twin subjects. Zetzsche and colleagues

(2006) studied a sample of patients with borderline personality disorder, with and without major depression, and found that those with major depression had significantly larger amygdalar volumes than did those without major depression. Moreover, there was a significant association between severity of depressive symptoms and left amygdalar volume. Although these findings generally depict a relation between increased amygdalar volume and depression, it is important to stress that (1) the causal relations between the two entities are still unknown, and (2) some inconsistencies among studies are present. Indeed, some researchers reported either decreased bilateral volume in the amygdalar core nuclei (Sheline, Gado, & Price, 1998) or null findings (Ashtari et al., 1999; Coffey et al., 1993; Pantel et al., 1997). Although the reasons are still unclear, it is interesting to note that two null findings were found in studies of geriatric depression (Ashtari et al., 1999; Pantel et al., 1997).

Functionally, abnormal elevations of resting rCBF 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 an FDG-PET study, Ho and colleagues (1996) reported increased absolute cerebral glucose metabolic activity in several brain regions, particularly the amygdala (+44%), in 10 unmedicated men with unipolar depression during a non-REM sleep period. Furthermore, in his review, Drevets (2001) reports data from five consecutive studies in which increased rCBF or glucose metabolism has been consistently replicated in depressives with familial MDD or melancholic features. In a postmortem study, serotonin ($5\text{-}HT_2$) receptor density was significantly increased in the amygdalas of depressive patients who committed suicide (Hrdina, Demeter, Vu, Sotonyi, & Palkovits, 1993).

Abnormally increased amygdalar activation has also been reported in bipolar depression (Ketter et al., 2001) and in anxiety disorders, which often show 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 (Abercrombie et al., 1998; Drevets et al., 1992). 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, patients with remitted MDD exhibiting symptom relapse as a consequence of serotonin depletion showed increased amygdalar activation prior to the depletion compared to those who did not relapse (Bremner, Randall, et al., 1997).

In one of the first fMRI studies using an activation paradigm, Yurgelun-Todd and colleagues (2000) reported higher left amygdalar activation for patients with BD than for controls in response to fearful faces. More recently, Fales and colleagues (2007) showed that a sample of 27 patients with major depression exhibited significantly greater activation in the amygdala in response to unattended fear-relevant stimuli compared with 24 healthy controls. Using a paradigm based on our prior studies of anticipatory anxiety (Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006), Abler, Erk, Herwig, and Walter (2007) found that in response to a cue that predicted a negative picture, depressed patients showed greater activation in the extended amygdalar region compared with controls. They also found that depression severity was positively correlated with ventral amygdalar activation in response to negative pictures. Three recent studies focused on emotional memory found evidence of amygdalar differences in depression during encoding. Ramel and col-

leagues (2007) found that amygdalar activation during encoding predicted recall of negative-valenced self-referent words in a subset of patients with remitted depression compared with never-depressed controls only in a condition that followed a sad mood induction, but not before the mood induction. In a sample of adolescents with major depression, Roberson-Nay and colleagues (2006) found that patients had greater left amygdalar activation compared with healthy controls during successful versus unsuccessful encoding of faces. Finally, distinguishing among difference valences of stimuli, Hamilton and Gotlib (2008) found that depressed adults were characterized by greater right amygdalar activation than were nondepressed controls during the encoding of subsequently recalled negative, but not positive or neutral, stimuli.

To probe individual differences in connectivity between the amygala and the vmPFC, which we previously found to be inversely coupled in healthy controls (Urry et al., 2006), we compared patients with major depression to a new sample of healthy controls (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007) on an emotion regulation task in the scanner. We replicated our previous finding of inverse coupling between the vmPFC and the amygdala in controls. Among depressed patients these brain regions were positively correlated. Moreover, measures of pupil dilation were obtained to index cognitive effort during emotion regulation. Although there was no main group effect on this measure, indicating that the patients and controls expended comparable effort to down-regulate their emotion, we did find a very different pattern of correlation between the pupil measures and brain activity. For the controls, the more effort they expended (as indexed by greater pupil dilation), the *less* the activation in emotion-related brain regions, such as the amygdala. However, for patients, this association was positive.

These latter findings suggest that one fundamental abnormality in depression may be associated with the regulation of negative affect. Despite what appear to be normal levels of effort and engagement, several of our findings suggest that such effort does not culminate in adaptive modulation of neural activity in emotion-processing regions. Our findings further suggest that there may be a subset of patients with depression who actually show exacerbations in symptoms during the voluntary regulation of negative affect. We believe that such strategies may be associated with rumination.

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 a speculation, this mechanism may rely on norepinephrine, which is (1) oftentimes abnormally elevated in depression (e.g., Veith et al., 1994); (2) involved in amygdala-mediated emotional learning (Ferry, Roozendaal, & McGaugh, 1999); and (3) affected by glucocorticoid secretion, which is often elevated in MDD (e.g., Carroll et al., 1976). Thus, these findings may explain cognitive biases toward aversive or emotionally arousing information observed in depression.

Increased amygdalar activation in depression may also represent a possible biological substrate for anxiety, which often is 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, because 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 of adversity (Schulkin, 1994).

Our findings on emotion regulation in depression raise the possibility that when abnormally high levels of amygdalar activation are observed in depression, they may reflect ab-

normalities in the modulation of amygdalar activity by regions of the PFC and, as such, reflect problems in emotion regulation. Although some data support this conjecture, additional research is needed to determine whether these are state or trait abnormalities, and to determine the specific profile of symptoms with which they may be associated.

SUMMARY AND FUTURE DIRECTIONS

In this chapter we have reviewed circuitry that underlies the representation and regulation of emotion. This circuitry 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 bidirectional 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 at present 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 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 or structural, or both. Future research should include measures of both functional (e.g., Cordes et al., 2000) and structural connectivity. The latter can be beautifully measured with diffusion tensor imaging (Le Bihan et al., 2001).

In the course of this review, we have drawn on the animal and human literature on basic processes in emotion and emotion regulation to help interpret the abnormalities 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 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 have 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 specifically in pregoal 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 amygdalar 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 op-

tions. According to an influential theory of ACC function (Carter et al., 1999), the ACC monitors the conflicts or cross-talk among brain regions. When such conflict is detected, the ACC issues a call for further processing to the PFC, which 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 (for a review, see Bush et al., 2000) 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 him or her in a particular social or role context. For example, dispositional mood state may predispose depressed individuals, to set few goals and engage in little intentional action, yet the demands of their environments may include expectations to behave and act in specific ways. In an individual with normal levels of ACC activation, the signal from ACC would call to other brain regions, the PFC being the most important, to resolve the conflict and to engage in appropriate goal-directed behavior. However, in an individual with abnormally low levels of ACC activation, the conflict between dispositional mood state and the expectations of context would not be effectively monitored; 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, as we noted earlier, 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 have been found to produce hippocampal cell death. In humans, various stress-related disorders, including depression, have been found to be associated with hippocampal atrophy. Whether such hippocampal volume differences are a cause or a consequence of the depression cannot be determined 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 hippocampus-dependent problem in the context modulation of emotional responses. We have shown such effects in rhesus monkeys (for a review, see Davidson, Jackson, & Kalin, 2000), though these effects 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 in a certain subtype of individual, contextual encoding is intact and PFC-implemented, goal-directed behavior is intact but context fails to guide and reprioritize goals adequately. In such cases, the functional and/or anatomical connectivity between hippocampus and PFC might be a prime candidate for dysfunction. As noted earlier, tools are now available to examine both types of connectivity with 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 noted earlier, 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, which enables 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 amygdalar activation both at baseline (Schaefer et al., 2000) and in response to challenge (for a review, see Davidson & Irwin 1999). Moreover, as we noted earlier, it is likely that regions of the PFC play an important role in modulating activation in the amygdala, thus influencing the time course of amygdala-driven, negative affective responding (Johnstone et al., 2007; Urry et al., 2006). In light of the reported associations between individual differences in amygdalar activation and affect measures, it is likely that when it occurs, hyperactivation of the amygdala in depression is associated more with fear-like and anxiety components of the symptoms than with sad mood and anhedonia. In our own work, we have found that amygdalar 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.

Several types of studies critically need to be performed in light of the extant evidence reviewed in this chapter. First, studies are needed 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 hypothesized to be implemented in those brain regions. Relatively few studies of this kind have been conducted. Most studies on depressed patients that examine relations between individual differences in neural activity and behavioral 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 explicitly designed to highlight the processes implemented in different parts of the circuit 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. This possibility underscores the real necessity of including measures of connectivity in future research.

As noted several times in this review, longitudinal studies of at-risk samples with the types of imaging measures featured in this review are crucial. We do not know whether any of the abnormalities we discussed, both of a structural and functional variety, precede the onset of the disorder, co-occur with the onset of the disorder, or follow after some time 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 we reviewed earlier showing a relation between the number of cumulative days depressed over the course of the lifetime and hippocampal volume suggest that this abnor-

mality may follow the expression of the disorder and represent a consequence rather than a primary cause of the disorder. Before such a conclusion is accepted, however, 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 strong support for the view that *depression* is 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 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 on the location and nature of the abnormality in the circuitry featured in this review. We believe that this ambitious effort will lead to considerably more consistent findings at the biological level and also enable us to characterize more rigorously different endophenotypes that could then be exploited for genetic studies.

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