PARSING THE SUBCOMPONENTS OF EMOTION AND DISORDERS OF EMOTION: PERSPECTIVES FROM AFFECTIVE NEUROSCIENCE

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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 individual differences in affective style, mood regulation, and mood disorders is helping to generate a new understanding of the brain circuitry underlying these phenomena. 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 on the understanding of normal and pathological individual differences in affective style, its constituent components, and their neural bases (see, e.g., Davidson, Jackson, & Kalin, 2000; Davidson, 2000).

Affective neuroscience takes as its overall aims a project that is similar to that pursued by its cognate discipline, cognitive neuroscience, though 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 since 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 individual differences in affective style since the key characteristic of variations in mood among individuals is the extent to which negative affect persists versus subsides rapidly. Moreover, these ideas have significant import for understanding disorders of mood. Some patients with mood disorders may have a particular problem with persistence of negative affect while other

patients may have a primary deficit 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). While the phenomenology of emotion provides critical information to the subject 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 subjects' conscious experience of the contents of their emotional states and traits, these no longer constitute the sole source of information about emotion.

Since there are recent reviews of the basic literature on the circuitry underlying emotion and emotion regulation (e.g., Davidson & Irwin, 1999; Davidson, Jackson, et al., 2000; Davidson, Putnam, & Larson, 2000; Rolls, 1999), these data will not be systematically reviewed in this chapter. We emphasize studies that have been published in the past three years since two recent reviews cover much of the literature prior to this time (Davidson, Abercrombie, Nitschke, & Putnam, 1999; Drevets, 1998). A major focus of this chapter will be on individual differences in affective style and how such variability across individuals can be captured using objective laboratory probes rather than relying exclusively upon self-report data.

We have two broad goals for this chapter:

1. To review the functional role of the prefrontal cortices, anterior cingulate, hippocampus, and amygdala in affect and emotion regulation (see Figure 2.1 for a depiction of these structures and their locations).
2. To review the functional and structural variations in these regions that have been linked to affective style and affective disorders.

The Circuitry of Emotion

Prefrontal Cortex (PFC)

PFC: Functional and Anatomical Considerations for Understanding Its Role in Affect

Although the prefrontal cortex is often considered to be the province of higher cognitive control, it has also consistently been linked to various features of affective processing (see, e.g., Nauta, 1971, for an early preview). Miller and Cohen (2001) have recently outlined a comprehensive theory of 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 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 where the arousal of emotion is inconsistent with other goals that are 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 the overall goals of the person. 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 disorders of emotional processing such as 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, Jackson, et al., 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, 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 where a dominant response set is established to respond quickly, except those trials on which a cue to inhibit the response is presented. Two recent studies using event-related 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, Ross, & Stein, 1999; Konishi et al., 1999).

Depressed individuals with hypoactivation in certain

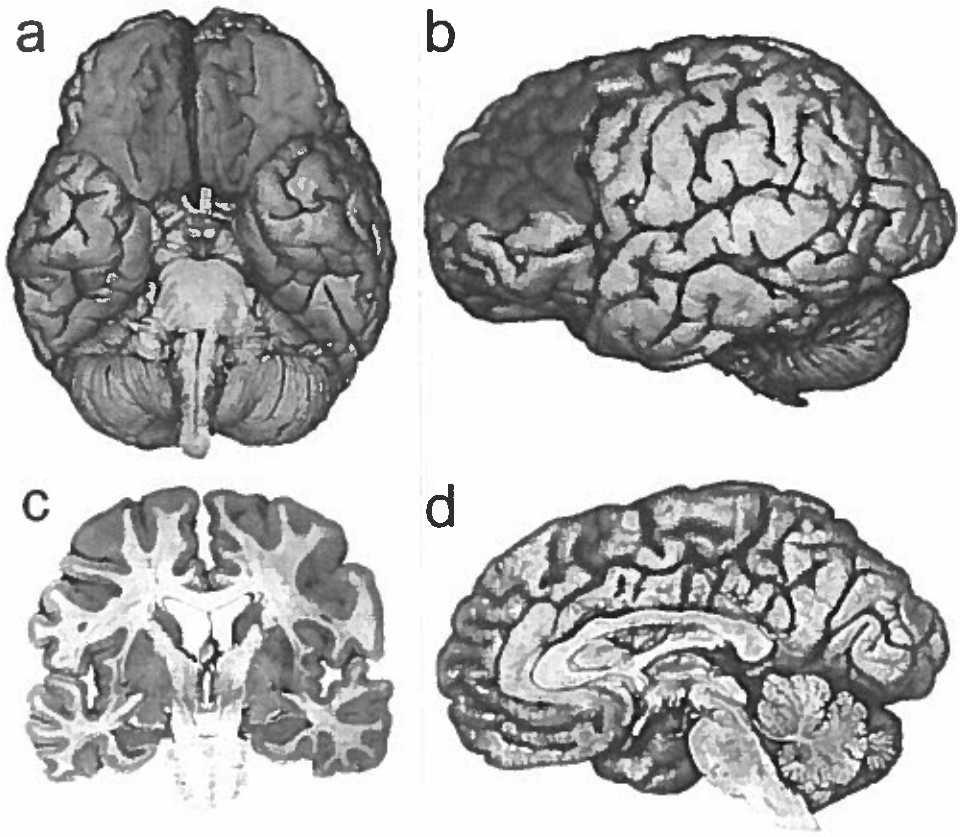

Figure 2.1 Key brain regions involved in affect and mood disorders. (A) Orbital prefrontal cortex (green) and the ventromedial prefrontal cortex (red). (B) Dorsolateral prefrontal cortex (blue). (C) Hippocampus (purple) and amygdala (orange). (D) Anterior cingulate cortex (yellow). (*See color insert.*)

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 where decision making is ambiguous and where the maintenance of goal-directed behavior is required in the face of potentially strong alternative responses. As we will 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 in particular 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, Kringelbach, Rolls, Hornak, & Andrews, 2001). In particular, a left-sided medial region of the oribitalfrontal cortex (OFC) appears particularly responsive to rewards while a lateral right-sided region appears particularly 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 differences among individuals in affective style. For example, there are individual differences in responsivity to rewards versus punishments that can probed behaviorally using signal detection methods (Henriques, Glowacki, & Davidson, 1994; Henriques & Davidson, 2000). Most normal individuals exhibit systematic modification of response bias to monetary reward, but some do not. Those who do not showed elevated depressed mood. We would also predict that left-medial OFC would be hyporesponsive to manipulations of reward in such individuals while right-lateral OFC to punishment would either be normal or perhaps accentuated.

Anterior Cingulate Cortex (ACC): Functional and Anatomical Considerations for Understanding Its Role in Affect

Several theories have proposed that the ACC acts as a bridge between attention and emotion (Devinsky, Morrell,

& Vogt, 1995; Ebert & Ebmeier, 1996; Mayberg, 1997; Vogt, Nimchinsky, Vogt, & Hof, 1995). In their recent 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, 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 (areas 25, 32, 33, and rostral area 24). The second, referred to as the "cognitive subdivision," involves dorsal regions of the ACC (caudal area 24' and 32', cingulate motor area). The affect subdivision possesses extensive connections with limbic and paralimbic regions—such as the amygdala, nucleus accumbens, OFC, periaqueductal 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. Owing to its strong connections with the lateral hypothalamus, the subgenual ACC (BA25) is considered the most important region within the frontal cortex for regulating autonomic function (Öngür, An, & Price, 1998).

Conversely, the cognitive subdivision is intimately connected with the DLPFC (BA46/9), posterior cingulate, parietal cortex (BA7), 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 (cognitive) ACC subdivisions is emerging (Bush et al., 1998; Bush, Luu, & Posner, 2000; Whalen et al., 1998; see Figure 2.2).

From a functional perspective, activation of the cognitive subdivision of the ACC has been reported during interference between competing information (Pardo, Pardo, Janer, & Kaichle, 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). 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

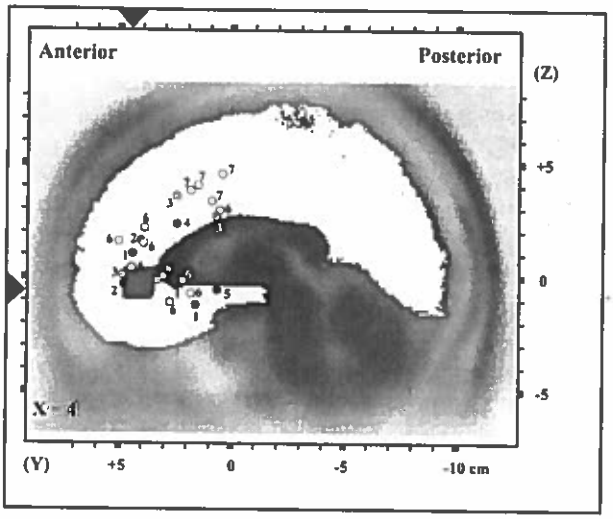

Figure 2.2 Summary of functional brain imaging studies of anterior cingulate cortex (ACC) involvement in depression as well as during various cognitive and affective task manipulations. Foci of ACC activation or deactivation were registered to a common stereotaxic brain atlas (Talairach & Tournoux, 1988) 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); 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). (*See color insert.*)

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 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 2.2).

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 or 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 where 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). Relatedly, it is not surprising that the ACC is one of the most consistently activated regions in patients with different anxiety disorders, such as OCD (Breiter et al., 1996; Rauch et al., 1997), simple phobia (Rauch et al., 1995), and 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; for review, Binder & Iskandar, 2000), possibly because of a reduction of conflict monitoring and uncertainty that otherwise characterize these psychiatric conditions.

The interplay between the affective and cognitive subdivision of the ACC is presently 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, Cummings, Galloway, & Malloy, 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 now replicated finding in depressed patients that increased *pre*-treatment activity in the rostral ACC is associated with eventual better treatment response (Mayberg et al., 1997; Ebert, Feistel, & Barocka, 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 six weeks showed higher pre-treatment glucose metabolism in a rostral region of the ACC (BA 24a/b) compared to 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. In other words, individuals exhibiting high levels of activation in the rostral ACC may be affectively resilient since these individuals would be motivated to resolve discrepancies between their current mood state and the behavior that is most appropriate for the situation at hand.

One of the major outputs from the ACC is a projection to 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. Individual differences in PFC function that are relevant to affective style may arise as a consequence of variations in signals from ACC, or may be intrinsic to the PFC, or both. There may ACC-based variations in affective style that may be reflected phenomenologically in the motivation or "will-to-change" certain habits or patterns of affective reactivity. Individuals with low levels of rostral ACC activation would not experience conflict between their current state and the demands of everyday life and would thus be unmotivated to alter their behavior. PFC-based variations in affective style may predominantly revolve around differences among individuals in the capacity to organize and guide behavior in a goal-directed fashion.

An important issue not considered above is the anatomical and functional connectivity between the different regions of PFC and ACC. Future studies need to examine both structural and functional variation in these connections since it is likely that some individual differences in affective style are primarily associated with connectivity between PFC, ACC, and amygdala, rather than with activation differences in any single or even multiple regions. We comment on this issue in more detail below.

Hippocampus: Functional and Anatomical Considerations for Understanding Its Role in Affect

The hippocampus is critically involved in episodic, declarative, contextual, and spatial learning and memory (Squire & Knowlton, 2000; Fanselow, 2000). Additionally, it is also importantly 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, Dolan, Armong, & 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-Jørgensen, & Pedersen, 2000), vocal expressions of fear (Phillips et al., 1998), aversive taste (Zald, Lee, Fluegel, & Pardo, 1998), anticipatory anxiety (Javanmard et al., 1999), procaine-induced affect (Ketter et al., 1996; Servan-Schreiber & Perlstein 1997), 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 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 the loved person (Bartels & Zeki, 2000). Also, hippocampal activation was correlated with long-term recognition memory for pleasant films (Hamann, Eby, Grafton, & Kitts, 1999).

In order 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 reevocation and consolidation of contextual information associated with similar situation in the past (see, e.g., Nader, Schafe, & LeDoux, 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, Friston, & Dolan, 1997; Morris, Ohman, & Dolan, 1999), even when the information is presented below the level of conscious awareness (Morris et al., 1999). As recently 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 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 long-term potentiation in the dentate gyrus. Although drawing conclusions from these rodent studies to humans is at this stage speculative, 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 & Perlstein, 1997; 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 interplay between these regions for modulating extinction of conditioned fear (Corcoran & Maren, 2001).

In their recent review, Davidson and colleagues (Davidson, Jackson, et al., 2000) noted that various form 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.

In a series of studies with non-human primates, Kalin and colleagues (Kalin & Shelton, 2000) have used the hu-

man intruder paradigm to probe the context specificity of emotional responding. In this paradigm, the monkey is exposed to different contexts that elicit a specific normative pattern of affective responses. In response to the profile of a human intruder (no eye contact, or NEC condition), the animals tend to freeze while in response to the same human staring at the animal, agonistic, aggressive behavior is elicited. When the animal is alone, freezing and aggression decline and the animals vocalize. These very well-defined normative patterns can be used to identify responses that are context-inappropriate. In a large group of monkeys (N = 100), approximately five show highly context-inappropriate responding. The most dramatic example of this is the small group of animals that freeze during the Alone condition at levels that are comparable to what they exhibit during the NEC condition. These are the animals that we predict would have hippocampal dysfunction since they are regulating their emotions in a context-appropriate fashion. These animals do have high levels of cortisol and extreme right-sided prefrontal activation derived from a noninvasive EEG measurement (see Figure 2.3).

Given the preclinical and functional neuroimaging literature reviewed above, one may hypothesize that subjects

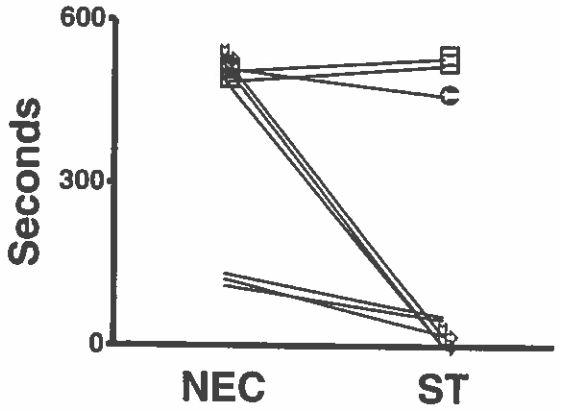

Figure 2.3 Freezing duration in seconds (out of a total of 600 seconds) in response to the No Eye Contact (NEC—exposure of the monkey to a profile of a human) and the Stare (ST) conditions in four groups of animals: One group shows very long durations of freezing during the normative context (NEC) but then freezes little during ST. Another group shows moderately elevated freezing during NEC and then shows little during ST. A third group shows virtually no freezing during either NEC or ST. Finally, the fourth group exhibits high levels of freezing in response to both NEC and ST. This is the group that displays out-of-context freezing (i.e., during ST). The group of three animals who show the out-of-context freezing are the only animals in a group of 100 to exhibit this pattern. From Kalin and Shelton (2000), copyright © 2000 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

displaying 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, Wang, Gado, Csernausky, & Vannier, 1996; Sheline, Sanghaui, Mintun, & Gado, 1999; Shah, Ebmeier, Glabus, & Goodwin, 1998; Bremner et al., 2000; von Gunten, Fox, Cipolotti, & Ron 2000; Steffens et al., 2000; Mervaala et al., 2000; but see Vakili et al., 2000; Ashtari et al., 1999), bipolar disorder (Noga, Vladar, & Torrey, 2001), posttraumatic stress disorder (Bremner et al., 1995; Bremner, Randall, et al., 1997; Stein, Koverola, Hanna, Torchia, & McClarty, 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 been also 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 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, 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 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. 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 life-time 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 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, & Mendela, 1976). Higher levels of cortisol may, in turn, lead to neuronal damage in the hippocampus, since this region possesses high levels of glucocorticoid receptors (Reul & De Kloet, 1986) and glucocorticoids are neurotoxic (Sapolsky, Krey, & McEwan, 1986). Since 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, Goodwin, & Chrousos, 1988; Sapolsky, Uno, Robert, & Finch, 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, 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 empirically verified in humans.

Although intriguing, these findings cannot inform us about the causality between hippocampal dysfunction, elevated levels of cortisol, and most important, inappropriate context-regulation of affect. 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, Rajkowska, Du, Seraji-Bozorgzad, & 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 environment (Kempermann, Kuhn, & Cage, 1997; see Gould, Tanepat, Rydel, & Hastings, 2000, for review). In humans, neurogenesis in the adult human hippocampus has been also 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 magnitude 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, 2000; Jacobs, Praag, & Gage, 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 context-modulation of affective responding and hippocampal function. Future studies should (1) assess whether hippocampal atrophy precedes or follows onset of depression or other sydromes of affective dysregulation; (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: Functional and Anatomical Considerations for Understanding Its Role in Affect

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, 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. 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 (see also Davis & Whalen, 2001; Holland & Gallagher, 1999; Whalen, 1998). Most stimuli in this class may be conceptualized as having an aversive valence since we tend to have a negativity bias in the face of uncertainty (Taylor, 1991).

Both structural and functional differences in the amygdala have been reported in disorders of emotion, particularly depression. Structurally, several recent studies re-

ported an association between enlargement of amygdala 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). In a recent study, Mervaala et al. (2000) observed significant asymmetry in amygdalar volumes (right smaller than left) in patients with major depressive disorder (MDD) but not in the controls. In TLE patients with dysthymia, left amygdala volume was positively correlated with depression severity, as assessed with the BDI (Tebartz van Elst et al., 1999). Although these findings 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 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 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 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-REM sleep period. Further, in his recent 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, 5-HT2 receptor density was significantly increased in the amygdala of depressive patients committing suicide (Hrdina, Demeter, Vu, Sotonyi, Palkovits, 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 at least in some subtypes of depression amygdalar dysfunction may be traitlike. Interestingly, remitted MDD patients showing symptom relapse as a consequence of serotonin depletion showed increased amygdalar activation *prior* to the depletion compared to those who will not relapse (Bremner, Innis, et al., 1997). Finally, in one of the first fMRI studies using an activation paradigm, 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 (1) is oftentimes abnormally elevated in depression (e.g., Veith et al., 1994), (2) is involved in amygdala-mediated emotional learning (Ferry, Roozendaal, & McGough, 1999), and (3) is 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 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 hand, 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, Drevets, & Price, 1998). 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 circuitry that underlies the representation and regulation of emotion. It is this circuitry that is responsible for many of the emotional variations among people and for governing vulnerability and resilience in the face of stressful events. 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. Variations in the morphometry and functioning of each of these structures have been reported in disorders of emotion, and functional variations are associated with several parameters of affective style in normal individuals. The establishment of differences in brain function or structure in cross-sectional studies that involve only a single assessment have been informative. However, such studies cannot specify which variations may be primary and which may be a consequence of primary variations. For example, an individual may have a low threshold for activation in the amygdala that will predispose him to react with more intense and more prolonged negative affect in response to a stressful event. Territories of the prefrontal cortex may display accentuated activation as part of a regulatory strategy to attenuate activation in the amygdala. In this instance, one might refer to the amygdala difference as primary and the PFC difference as secondary. In the absence of longitudinal research, however, it will be difficult to tease apart.

In addition, a paucity of work has examined functional and/or structural connectivity among these regions. Some of the variations in affective style that have been identified may arise as a consequence of variations in 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 normal and pathological variations in affective style 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 while 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 pre-goal attainment forms of positive affect while 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 since subjects are participating in a scientific experiment, yet there are the responses that are pulled for by the emotional challenge, such as certain patterns of facial expression. This is commonly reported by subjects and is associated with ACC activation. The ACC is also activated when an individual is exposed to a conflict among different channels of emotional communcation. For example, when the face and voice each express inconsistent emotions simultaneously, a conflict in the viewer is created and the ACC is activated (Dolan, Morris, & de Gelder, 2001). Individuals with low levels of ACC activation would be expected to be less sensitive to or less reactive to these inconsistent affective cues.

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 and act in spe-

cific 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 have been found to produce hippocampal cell death. In humans, various stress-related disorders, including depression, have been found to be 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, Jackson, et al., 2000, a for review) though they have not yet been studied systematically in humans. 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 and other disorders of emotion. 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. In our own work, 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 critically need to be performed in light of the extant evidence reviewed in this chapter. First, studies are needed that relate specific variations in activation 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. Relatively few studies of that kind have been conducted. Most studies that examine relations between individual differences in neural activity and affective style, either normal or abnormal, almost always relate such neural variation to 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 variations discussed above, both of a structural and a functional variety, precede the onset of a disorder, co-occur with the onset of a disorder or follow by some time the expression of a 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. For example, data showing a relation between the number of cumulative days depressed over the course of the lifetime and hippocampal volume (Sheline et al., 1996, 1999) 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 specific constituents of emotion regulation and affective style will be identified that have not been directly uncovered with self-report methods. For example, the rapidity of recovery from a stressful stimulus or variations in context-sensitivity of emotional responding are each separable processes that will influence self-reports of emotion, yet such reports will not be revealing with respect to the constituents that led to these influences. Thus, two individuals who each report high levels of dispositional negative affect may be doing so because of variations in different parts of the circuitry reviewed. It is also very likely that some of the important variations in affective style, such as individual differences in the rapidity of recovery from a negative event, may not map precisely onto extant personality or self-report descriptors. A major challenge for the future will be to build a more neurobiologically plausible scheme for parsing the heterogeneity of emotion, emotion regulation, disorders of emotion, and affective style, based on 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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