Anxiety and Affective Style: Role of Prefrontal Cortex and Amygdala

Richard J. Davidson

This article reviews the modern literature on two key aspects of the central circuitry of emotion: the prefrontal cortex (PFC) and the amygdala. There are several different functional divisions of the PFC, including the dorsolateral, ventromedial, and orbital sectors. Each of these regions plays some role in affective processing that shares the feature of representing affect in the absence of immediate rewards and punishments as well as in different aspects of emotional regulation. The amygdala appears to be crucial for the learning of new stimulus–threat contingencies and also appears to be important in the expression of cue-specific fear. Individual differences in both tonic activation and phasic reactivity in this circuit play an important role in governing different aspects of anxiety. Emphasis is placed on affective chronometry, or the time course of emotional responding, as a key attribute of individual differences in propensity for anxiety that is regulated by this circuitry. Biol Psychiatry 2002;51: 68–80 © *2002 Society of Biological Psychiatry*

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Introduction

Biobehavioral scientists are increasingly recognizing the importance of emotion for the fundamental tasks of survival and adaptation (Damasio 1994; Ekman and Davidson 1994; Pinker 1997). Emotion modulates memory, facilitates decision making, influences learning, and provides the motivation for critical action in the face of environmental incentives. Emotion is also the stuff of individual differences. It is a key component, if not the major ingredient, for many of the fundamental dimensions of personality and vulnerability factors that govern risk for psychopathology (Davidson and Irwin 1999a; Davidson 2000a). In this article, evidence on the role of the prefrontal cortex (PFC) and amygdala as key structures in a circuit that govern positive and negative affect and affective style will be reviewed, with an emphasis on mechanisms responsible for individual differences in vulnerability to anxiety disorders. It should be noted at the outset that these brain regions are part of a larger circuit that includes the anterior cingulate, hippocampus, and insula, each of which contribute uniquely to subcomponents of emotion and variations in affective style (see Davidson et al 2000b).

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The Central Circuitry of Emotion

The Prefrontal Cortex

Though approaching the topic from very different perspectives, a growing body of literature is converging on the idea that there exist two fundamental systems that underlie approach and withdrawal–related emotion and motivation, or positive and negative affect (Cacioppo and Gardner 1999; Davidson and Irwin 1999a; Gray 1994; Lang et al 1990; Schnierla 1959). The precise description of these systems differs somewhat across investigators as does the anatomical circuitry that is featured, but the essential elements are quite similar in each of these different proposals. The approach system has been described by Davidson and Irwin (1999a) as facilitating appetitive behavior and generating particular types of positive affect that are approach-related, such as the emotion occurring as an organism moves closer toward a desired goal. The withdrawal system, on the other hand, facilitates the withdrawal of an organism from sources of aversive stimulation and/or organizes appropriate responses to cues of threat. This system also generates withdrawal-related negative emotions, such as disgust and fear. A variety of evidence indicates that these systems are implemented in partially separable circuits, and it is to this evidence that we now turn. Our focus will be on two key components of this circuitry: the PFC and the amygdala. For more extensive discussion of this entire circuitry, including other regions not considered here, see Davidson and Irwin (1999a).

A large corpus of data at both the animal and human levels implicate various sectors of the PFC in emotion.

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The PFC is not a homogeneous zone of tissue but rather has been differentiated on the basis of both cytoarchitectonic as well as functional considerations. The three subdivisions of the primate PFC that have been consistently distinguished include the dorsolateral, ventromedial, and orbitofrontal sectors. In addition, there appear to be important functional differences between the left and right sides within each of these sectors.

The case for the differential importance of left and right PFC sectors for emotional processing was first made systematically in a series of studies on patients with unilateral cortical damage (Gainotti 1972; Robinson et al 1984; Sackeim et al 1982). Each of these studies compared the mood of patients with unilateral left- or right-sided brain damage and found a greater incidence of depressive symptoms following left-sided damage. In most cases, the damage was fairly gross and likely included more than one sector of PFC and often included other brain regions as well. The general interpretation that has been placed upon these studies is that depressive symptoms are increased following left-sided anterior PFC damage, because this brain territory participates in a process that underlies certain forms of positive affect and when damaged, leads to deficits in the capacity to experience positive affect, a hallmark feature of depression (Watson et al 1995). Though most of the extant lesion data are consistent with this general picture (see Robinson and Downhill 1995 for a review), some inconsistencies have also appeared (e.g., Gainotti et al 1993; House et al 1990). Davidson (1993) has reviewed in detail these studies and has addressed a number of critical methodological and conceptual concerns in this literature. The most important of these issues is that according to the diathesis–stress model of anterior activation asymmetry proposed by Davidson and colleagues (e.g., Davidson 1995, 1998b; Henriques and Davidson 1991), individual differences in anterior activation asymmetry, whether lesion-induced or functional, represent a diathesis. As such, they alter the probability that specific forms of emotional reactions will occur in response to the requisite environmental challenge. In the absence of such a challenge, the pattern of asymmetric activation will simply reflect a propensity but will not necessarily culminate in differences in mood or symptoms. In a recent study with the largest sample size to date (n = 193) for a study of mood sequelae in patients with unilateral lesions, Morris et al (1996) found that among stroke patients, it was only in those with small-sized lesions that the relation between left PFC damage and depressive symptoms was observed. It is likely that larger lesions intrude on other brain territories and mask the relation between left PFC damage and depression.

A growing corpus of evidence in normal intact humans is consistent with the findings derived from the lesion evidence. Davidson and his colleagues have reported that induced positive and negative affective states shift the asymmetry in prefrontal brain electrical activity in lawful ways. For example, film-induced negative affect increases relative right-sided prefrontal and anterior temporal activation (Davidson et al 1990), whereas induced positive affect elicits an opposite pattern of asymmetric activation. Similar findings have been obtained by others (e.g., Ahern and Schwartz 1985; Jones and Fox 1992; Tucker et al 1981). In addition, we will review in the next section a body of evidence that supports the conclusion that individual differences in baseline levels of asymmetric activation in these brain regions are associated with dispositional affective style. Using an extended picture presentation paradigm designed to evoke longer-duration changes in mood (Sutton et al 1997a), we measured regional glucose metabolism with positron emission tomography (PET) to ascertain whether similar patterns of anterior asymmetry would be present using this very different and more precise method to assess regional brain activity (Sutton et al 1997b). During the production of negative affect, we observed right-sided increases in metabolic rate in anterior orbital, inferior frontal, middle, and superior frontal gyri, whereas the production of positive affect was associated with a pattern of predominantly left-sided metabolic increases in the pre- and postcentral gyri. Using PET to measure regional cerebral blood flow, Hugdahl and his colleagues (Hugdahl 1998; Hugdahl et al 1995) reported a widespread zone of increased blood flow in the right PFC, including the orbitofrontal and dorsolateral cortices and inferior and superior cortices during the extinction phase after learning had occurred compared with the habituation phase, before the presentation of the experimental contingencies.

Other investigators have used clinical groups to induce a stronger form of negative affect in the laboratory than is possible with normal control subjects. One common strategy for evoking anxiety among anxious patients in the laboratory is to present them with specific types of stimuli that are known to provoke their anxiety (e.g., pictures of spiders for spider phobics; making a public speech for social phobics). Davidson et al (2000a), in a study using brain electrical activity measures, have recently found that when social phobics anticipate making a public speech, they show large increases in right-sided anterior activation. Pooling across data from three separate anxiety disordered groups, Rauch et al (1997) found two regions of the PFC that were consistently activated across groups: the right inferior PFC and right medial orbital PFC.

The ventromedial PFC has been implicated in the anticipation of future positive and negative affective consequences. Bechara and his colleagues (Bechara et al 1994) have reported that patients with bilateral lesions of

the ventromedial PFC that also included some intrusion into the orbital frontal cortex have difficulty anticipating future positive or negative consequences, although immediately available rewards and punishments do influence their behavior. Such patients show decreased levels of electrodermal activity in anticipation of a risky choice compared with control subjects, whereas control subjects exhibit such autonomic change before they explicitly know that it is a risky choice (Bechara et al 1996, 1997, 1999).

The findings from the lesion method when effects of small unilateral lesions are examined and from neuroimaging studies in normal subjects and patients with anxiety disorders converge on the conclusion that increases in right-sided activation in various sectors of the PFC are associated with increased negative affect. Less evidence is available for the domain of positive affect, in part because positive affect is much harder to elicit in the laboratory. The findings from Bechara et al on the effects of ventromedial PFC lesions on the anticipation of future positive *and* negative affective consequences are based on studies of patients with bilateral lesions. It will be of great interest in the future to examine patients with unilateral ventromedial lesions to ascertain whether valence-dependent asymmetric effects are present for this sector of PFC as well.

Systematic studies designed to disentangle the specific role played by various sectors of the PFC in emotion are lacking. Many theoretical accounts of emotion assign it an important role in guiding action and organizing behavior toward the acquisition of motivationally significant goals (e.g., Frijda 1994; Levenson 1994). This process requires that the organism have some means of representing affect in the absence of immediately present rewards and punishments and other affective incentives. Such a process may be likened to a form of affective working memory. It is likely that the PFC plays a key role in this process (see e.g., Watanabe 1996). Damage to certain sectors of the PFC impair an individual's capacity to anticipate future affective outcomes and consequently result in an inability to guide behavior in an adaptive fashion. Such damage is not likely to disrupt an individual's responding to immediate cues for reward and punishment, only the anticipation before and sustainment after an affective cue is presented. This proposal can be tested using current neuroimaging methods (e.g., functional magnetic resonance imaging [fMRI]) but has not yet been rigorously evaluated. With regard to the different functional roles of the dorsolateral and ventromedial sectors of the PFC, Davidson and Irwin (1999a) suggested on the basis of considering both human and animal studies, that the latter sector is most likely involved in the representation of elementary positive and negative affective states in the absence of immediately present incentives, whereas the former sector is most directly involved in the representation of goal states toward which these more elementary positive and negative states are directed. Although the dorsolateral PFC is not typically viewed as a prefrontal sector that is connected with emotion and motivation, recent single unit work strongly supports this view. Hikosaka and Watanabe (2000) recorded from single neurons in the orbital and dorsolateral PFC in monkeys during a delay period while they anticipated reward. Neurons in both the orbital and dorsolateral sectors of the PFC showed delay period activity that varied with the nature of the reward. The difference between the properties of neurons in the dorsolateral and orbital PFC was that the former showed delay period activity that varied as a function of both spatial working memory and reward expectation, whereas the latter exhibited reward-dependent variation only. Hikosaka and Watanabe (2000) suggest that because the connections between the lateral PFC and amygdala are sparse (Barbas 1995), the processes related to reward expectation may first occur in the orbital frontal cortex and then information be transmitted to the lateral PFC, where integration of emotional and cognitive operations would occur.

The Amygdala

A large corpus of research at the animal—mostly rodent—level has established the importance of the amygdala for emotional processes (e.g., Aggleton 1993; Cahill and McGaugh 1998; LeDoux 1996). Because many reviews of the animal literature have appeared recently, a detailed description of these studies will not be presented here. LeDoux and his colleagues have marshaled a large corpus of compelling evidence to suggest that the amygdala is necessary for the establishment of conditioned fear. Whether the amygdala is necessary for the expression of that fear following learning and whether the amygdala is the actual locus where the learned information is stored is still a matter of some controversy (Cahill et al 1999; Faneslow and LeDoux 1999). Also not resolved is the extent to which the amygdala participates in all learning of stimulus-incentive associations, both negative and positive, and whether there are functional differences between the left and right amygdala (Davidson and Irwin 1999a). The classic view of amygdala damage in nonhuman primates resulting in major affective disturbances as expressed in the Kluver-Bucy syndrome where the animal exhibits abnormal approach, hyper-orality and sexuality, and little fear, is now thought to be a function of damage elsewhere in the medial temporal lobe. When very selective excitotoxic lesions of the amygdala are made that preserve fibers of passage, nothing resembling the Kluver-Bucy syndrome is observed (Kalin et al 2001; Meunier et

al 1999). The upshot of this diverse array of findings is to suggest a more limited role for the amygdala in certain forms of emotional learning, though the human data imply a more heterogeneous contribution.

Although the number of patients with discrete lesions of the amygdala is small, they have provided unique information on the role of this structure in emotional processing. A number of studies have now reported specific impairments in the recognition of facial expressions of fear in patients with restricted amygdala damage (Adolphs et al 1995, 1996; Broks et al 1998; Calder et al 1996). Recognition of facial signs of other emotions was found to be intact. In a study that required subjects to make judgments of trustworthiness and approachability of unfamiliar adults from facial photographs, patients with bilateral amygdala damage judged the unfamiliar individuals to be more approachable and trustworthy than did control subjects (Adolphs et al 1998). Recognition of vocalic signs of fear and anger was found to be impaired in a patient with bilateral amygdala damage (Scott et al 1997), suggesting that this deficit is not restricted to facial expressions. Other researchers (Bechara et al 1995) have demonstrated that aversive autonomic conditioning is impaired in a patient with amygdala damage, despite the fact that the patient showed normal declarative knowledge of the conditioning contingencies. Collectively, these findings from patients with selective bilateral destruction of the amygdala suggest specific impairments on tasks that tap aspects of negative emotion processing. Most of the studies have focused on the perceptual side, where the data clearly show the amygdala to be important for the recognition of cues of threat or danger. The conditioning data also indicate that the amygdala may be necessary for acquiring new implicit autonomic learning of stimulus–punishment contingencies. In one of the few studies to examine the role of the amygdala in the expression of already-learned emotional responses, Angrilli and colleagues (Angrilli et al 1996) reported on a patient with a benign tumor of the right amygdala in an emotion-modulated startle study. Among control subjects, they observed the well-known effect of startle potentiation during the presentation of aversive stimuli. In the patient with right amygdala damage, no startle potentiation was observed in response to aversive versus neutral stimuli. These findings suggest that the amygdala might be necessary for the expression of already learned negative affect.

Since 1995, a growing number of studies using PET and fMRI to investigate the role of the amygdala in emotional processes have begun to appear. Many studies have reported activation of the amygdala detected with either PET or fMRI when anxiety-disordered patients have been exposed to their specific anxiety-provoking stimuli compared with control stimuli (e.g., Breiter et al 1996a; Rauch et al 1996). When social phobics were exposed to neutral faces, they showed activation of the amygdala comparable to what was observed in both the phobics and control subjects in response to aversive compared with neutral odors (Birbaumer et al 1998). Consistent with the human lesion data, a number of studies have now reported activation of the amygdala in response to facial expressions of fear compared with neutral, happy, or disgust control faces (Breiter et al 1996b; Morris et al 1996; Phillips et al 1997). In the Breiter et al (1996b) fMRI study, they observed rapid habituation of the amygdala response, which may provide an important clue to the time-limited function of the amygdala in the stream of affective information processing. In a recent study, Whalen and his colleagues (Whalen et al 1998) observed activation of the amygdala in response to masked fear faces that were not consciously perceived. Unpleasant compared with neutral and pleasant pictures have also been found to activate the amygdala (Irwin et al 1996; Lane et al 1997). Finally, a number of studies have reported activation of the amygdala during early phases of aversive conditioning (Buchel et al 1998; LaBar et al 1998; Morris et al 1998). Amygdala activation in response to several other experimental procedures for inducing negative affect has been reported, including unsolvable anagrams of the sort used to induce learned helplessness (Schneider et al 1996), aversive olfactory cues (Zald and Pardo 1997), and aversive gustatory stimuli (Zald et al 1998). Other data on individual differences in amygdala activation and their relation to affective style will be treated in the next section.

The findings from both the lesion studies and neuroimaging on the role of the amygdala in affective processes raise a number of important questions about the functional significance of amygdala activation and precise role this structure may play in human emotion. One key question is whether the amygdala is implicated in all emotion, negative affect in particular or fear most specifically. Most neuroimaging studies that have induced actual emotion find greater amygdala activation to negative compared with positive elicitors. In a study of the effects of cocaine on cocaine addicts, Breiter et al (1997) report significant deactivation in the amygdala during self-reported “highs” following the administration of cocaine. Of the studies that have examined amygdala activation in response to facial expressions, all have consistently found greater activation in response to fear compared with other emotional faces, though a complete range of other emotions has not been sampled. Whalen (1999) has interpreted these data within a model that assigns a primary role for the amygdala in the detection of ambiguity. According to this model, preferential activation of the amygdala is observed in response to fear versus anger faces, because the former convey

threat though the source of the threat is ambiguous, whereas angry faces convey a threat but the source of the threat is unambiguous. Although some data are consistent with this view, other data indicating that bilateral destruction of the amygdala impairs recognition of both fear and anger vocal expression (Scott et al 1997) are not. Other recent human imaging findings, however, suggest that the amygdala may be importantly involved in positive affect as well. For example Beauregard and his colleagues (Beauregard et al 2001) used fMRI to measure activations produced by erotic film clips in normal male subjects and found activation in the amygdala, anterior temporal pole, and hypothalamus during a passive viewing condition.

Another important question raised but not answered by the new findings on the amygdala is whether there are reliable functional asymmetries in this region. During the experimental arousal of negative affect, some investigators report changes in activation in the left amygdala (e.g., Schneider et al 1997), some report changes in the right amygdala (e.g., Rauch et al 1996) and some report bilateral changes (e.g., Irwin et al 1996). Morris et al (1998) have proposed on the basis of a masking study that the right amygdala is involved in unconscious processing of emotional learning, whereas the left amygdala is more involved in conscious emotional learning. There are data at the rodent level that suggest that there might be important functional differences between left versus right amygdala lesions (Coleman-Mesches and McGaugh 1995a, 1995b). One crucial issue in the human neuroimaging literature is the need to perform the proper statistical comparisons to ascertain whether true asymmetric effects are present. This requires a test of the interaction between Condition and Hemisphere. Virtually none of the studies in the human neuroimaging literature have performed this crucial test (see Davidson and Irwin 1999b for an extensive discussion of this issue).

Finally, an issue left unaddressed in the human data is whether the amygdala is required for the ongoing expression of affect or whether it is specifically involved in only the initial acquisition of emotional learning. The fact that amygdala activation is present during early phases of conditioning and then appears to rapidly habituate (Buchel et al 1998; LaBar et al 1998) is consistent with the idea that the amygdala may be required only in the initial stages of learning. We (Kalin et al 2001) have recently performed studies in rhesus monkeys tested before and after very discrete excitotoxic lesions of the amygdala, which preserve fibers of passage and destroy only cell bodies. Complete destruction of the amygdala in these animals results in a dramatic attenuation of behavioral signs of fear in response to a snake; however, such lesions do not have any noticeable impact on freezing in response to a human intruder paradigm (see Kalin and Shelton 1989), nor do the lesions affect any of the biological correlates that have been found to be associated with an anxious endophenotype, including right prefrontal electroencephalogram (EEG) activation or high levels of baseline cortisol (Kalin et al 1998). Collectively, these findings imply that the amygdala may be crucial for learning new stimulus–threat contingencies and may be important in the expression of cue-specific fear; however, the amygdala does not appear to be necessary for the expression of already acquired individual differences in temperament or affective style.

Affective Style

Davidson (1992, 1998a) has used the term affective style to refer to the broad range of individual differences in different subcomponents of affective reactivity and dispositional mood. This is a very global term, and it is imperative to specify with more precision which particular system one is measuring affective reactivity in and which subcomponent of reactivity is being targeted for study. For example, one could measure affective reactivity in different response systems by using startle magnitude, MR signal change in the amygdala, or ratings on a self-report scale as the measure. Each of these obviously reflects activity in very different systems, and activation in these systems will not necessarily cohere. What is meant by subcomponent of reactivity has been articulated in detail in Davidson (1998a) and includes the following parameters: tonic level, threshold to respond, peak or amplitude of response, rise time to peak of response, and recovery time. These are not meant to necessarily reflect an exhaustive list of subcomponents; they are merely offered as examples. Each of these subcomponents can potentially be studied in different response systems, leading to many parameters of affective style. We know virtually nothing about the psychometric characteristics of measures of these different parameters, except for self-report measures (for two recent efforts examining different subcomponents of affective style in two different physiologic response systems, see Larson et al 2000; Tomarken et al 1992b), though this information is crucial if we are to develop rigorous measures of these constructs. In this section, we review data on the contributions of individual differences in prefrontal and amygdala function to affective style.

In two decades of previous research, we have performed a large number of studies designed to examine the role of activation asymmetries in prefrontal cortex and other anterior cortical zones in aspects of affective style. This work has been reviewed recently (Davidson 1995, 1998a, 2000a,b), and only highlights will be presented here. Using measures of scalp-recorded brain electrical activity, we found that indices of activation asymmetry based on power spectral measures were stable over time and exhib-

ited excellent internal consistency reliability (Tomarken et al 1992b) thus fulfilling a number of important psychometric criteria for an index of a traitlike construct. In a series of studies, we found that there are large individual differences in the magnitude and direction of baseline asymmetric activation in brain electrical activity measures obtained from prefrontal scalp regions in both infants (Davidson and Fox 1989) and adults (Davidson and Tomarken 1989). In 10-month old infants we found that those with greater relative right-sided prefrontal activation in prefrontal scalp regions were more likely to cry in response to a brief period of maternal separation compared with their left-activated counterparts (Davidson and Fox 1989). In toddlers and young children, we have observed that those individuals with greater relative right-sided prefrontal activation show more behavioral inhibition and wariness measured through laboratory-based behavioral observation (Davidson and Rickman 1999). In adults, we have found that individual differences in such measures predict dispositional mood (Tomarken et al 1992a), self-report measures of behavioral activation and inhibition (Sutton and Davidson 1997), repressive defensiveness (Tomarken and Davidson 1994), reactivity to positive and negative emotion elicitors (Tomarken et al 1990; Wheeler et al 1993), baseline immune function (Kang et al 1991), and reactivity of the immune system to emotional challenge (Davidson et al 1999b). In recent work (Larson et al 1998) we found that individual differences in electrophysiological measures of prefrontal asymmetry predicted the magnitude of recovery following a negative affective stimulus. These data suggest that the prefrontal cortex may play a role in regulating the timecourse of emotional responding and/or in the active inhibition of negative affect.

We have also found that individual differences in these brain electrical measures of anterior asymmetry are associated with mood and anxiety disorders. In particular, we have found that depressed subjects and individuals who are currently euthymic but have a history of past depression exhibit less left prefrontal activation compared with never-depressed control subjects (Henriques and Davidson 1990, 1991). We have also found that when social phobics anticipate making a public speech, they show large increases in right-sided prefrontal activation, though they do not differ from control subjects at baseline (Davidson et al 2000).

In a series of studies with Kalin (Davidson et al 1992, 1993; Kalin et al 1998), we have demonstrated that similar activation asymmetries can be measured in rhesus monkeys and that they predict similar types of behavior and biology as we observe in humans. In the most recent efforts of this kind, we found that animals with greater relative right-sided prefrontal activation exhibit higher basal levels of the stress hormone cortisol (Kalin et al 1998) and higher cerebrospinal fluid levels of corticotropin-releasing hormone (Kalin et al 2000). Similar data have recently been reported in humans (Buss et al 1997).

Recent studies in rodents also have uncovered asymmetries in prefrontal function that closely resemble those that have been studied in humans and nonhuman primates. Of most relevance to the work summarized above, Sullivan and Gratton (1999) reported that in acutely restrained rats, right or bilateral but not left medial prefrontal cortical lesions decreased corticosterone levels. Stress ulcer development after a single cold restraint stress was greatly reduced by either right or bilateral medial PFC lesions but was unaffected by left-sided lesions. These authors conclude that their data "suggest a preferential role for the right [medial] PFC in activating physiologic stress responses" (p. 2839).

A number of our original EEG observations have now been independently replicated by others (Ahern and Schwartz 1985; Allen et al 1993; Dawson et al 1992; Fox 1991; Harmon-Jones and Allen 1997; Jacobs and Synder 1996; Wiedemann et al 1999), though a few studies have appeared reporting only partial replications of aspects of our original findings (Hagemann et al 1998; Reid et al 1998). Davidson (1998b) has called attention to a number of crucial methodological and conceptual issues in these replication attempts and suggests that the difficulties in replication are at least in part a function of significant methodological limitations; however, it is also clear that with respect to asymmetries associated with mood and anxiety disorders, considerable heterogeneity exists in the forms of these psychopathologies, only some of which would be expected to show differences in prefrontal asymmetries compared with control subjects. Moreover, few studies using neuroimaging to address the role of prefrontal asymmetries in affective processes have appeared. As noted by Davidson and Irwin (1999a), only a very small handful of studies using PET or fMRI have conducted the proper statistical comparison to uncover asymmetry effects in their data. They (Davidson and Irwin 1999a) comment on the complexity of performing these analyses. Because the structural anatomy is not symmetrical, particularly for cortical tissue, it is very difficult to extract homologous regions for asymmetry analyses. The size of the regions may differ on the two sides of the brain, the anatomical homologue may not be in exactly the same location in each hemisphere, and the shape of the cortical territory on each side of the brain is often different. These facts present formidable methodological obstacles when using neuroimaging to make inferences about patterns of asymmetric activation.

The data from the Larson et al (1998) study referred to

above indicated that individuals with greater relative left-sided prefrontal activation at baseline have greater recovery of startle potentiation following the offset of a negative stimulus. Moreover, the measure of asymmetric prefrontal activation accounted for more variance in the magnitude of startle postnegative-stimulus offset (i.e., startle recovery) than it did during the stimulus. These findings imply that individual differences in prefrontal activation asymmetry may play a role in regulating the time course of emotional responding and that those individuals with more left-sided prefrontal activation may recover more quickly from negative affect or stress than their right-activated counterparts.

A clue to the mechanism that may underlie this consequence of left prefrontal activation is provided by a study from LeDoux's laboratory, where they found that rats with lesions of the medial prefrontal cortex show dramatically slower extinction of a learned aversive response compared with sham operated control subjects (Morgan et al 1993; but see Gewirtz et al 1997). These findings imply that there is a descending pathway between the medial PFC and the amygdala (Amaral et al 1992) that is inhibitory and thus represents an active component of extinction. In the absence of this normal inhibitory input, the amygdala remains unchecked and continues to remain activated. Whether this inhibitory input from the medial PFC is an important component of the prominent habituation observed in the amygdala remains to be clarified. Davidson (1998a) has suggested that in humans and possibly other primates, the major inhibitory influence on the amygdala may derive from the left prefrontal cortex. Consistent with this idea, recent PET findings suggest that in normal human subjects, glucose metabolism in the left medial and lateral prefrontal cortex is reciprocally coupled to metabolic activity in the amygdala, such that those subjects with decreased left prefrontal metabolic rate have increased metabolic rate in the amygdala (Abercrombie et al 1996). We propose that this mechanism may be responsible for the failure to recover quickly from negative events and the lengthening of its time course in those individuals who appear to be more vulnerable. Such an affective style may be associated a predisposition to develop anxiety disorders.

The two key features of the circuitry underlying positive and negative affect highlighted in this review are the PFC and the amygdala. In the section above, studies on the basic function of the amygdala in affective behavior were considered. Here the question is raised about individual differences in amygdala function and its relation to affective style. Although most research on the amygdala has emphasized its phasic function, there is a tonic level of activation in the amygdala that can be assessed with PET measures of regional glucose metabolism. Using MRI-based coregistration, we can draw regions-of-interest around the amygdala on an MR scan coregistered to the PET image and extract metabolic activity in such small regions without using any spatial filtering of the PET image. This provides higher resolution than could ordinarily be achieved using conventional cross-subject aggregation methods that require spatial smoothing of the images (see Abercrombie et al 1998; Schaefer et al 2000). Using such procedures, we have found that individual differences in metabolic activity in the right amygdala in particular predict dispositional negative affect on the Positive and Negative Affect Schedule (PANAS; Watson et al 1988) in a group of depressed patients (Abercrombie et al 1998). Using the same measure of negative affect, we (Irwin et al, unpublished data) have also found MR signal change in the amygdala in response to negative versus neutral stimuli accounts for a substantial amount of variance in PANAS trait negative affect scores ($r = .63$). Other researchers have found that individual differences in right amygdala glucose metabolic rate in response to emotional films predict the recall of negative emotional films assessed 3 weeks following the PET procedure. Those individuals with higher levels of glucose metabolism in the right amygdala recalled more of the negative film clips (Cahill et al 1996). Other investigators using both PET (Furmark et al 1997) and fMRI (LaBar et al 1998) reported that those subjects with greater activation in the amygdala during classic aversive conditioning showed greater evidence of electrodermal conditioning. Ketter et al (1996) using the anesthetic procaine as a pharmacological challenge reported that those individuals who had a dysphoric response to the drug had significantly greater activation of the amygdala compared with subjects exhibiting a euphoric response. Moreover, amygdala blood flow correlated positively with fear and negatively with euphoria on self-report measures of emotional intensity.

Some of the data reviewed above on relations between amygdala activation and dispositional negative affect appear at least on the surface to be inconsistent with the animal and human neuroimaging data reviewed above implying that the amygdala is important only in the initial learning of stimulus–threat associations but not in the expression of preexisting temperamental variation, such as behavioral inhibition. For example, in our own data using PET-derived measures of glucose metabolism in the amygdala (Abercrombie et al 1998), we found that subjects with greater metabolic rate in the right amygdala report higher levels of dispositional negative affect as assessed by the PANAS. A similar association was found using the identical affect measure with fMRI where subjects showing larger MR signal increases in the amyg-

dala in response to negative versus neutral pictures reported higher levels of dispositional negative affect. The PANAS requires subjects to rate a series of single-word adjectives on a 1–5 point scale to indicate the extent to which that emotion is present during their daily life. Thus, in these experiments, it appears that activation levels in the amygdala are associated with the expression of a preexisting affective style. We believe the key to resolving this apparent inconsistency among these findings lies in a more in-depth understanding of the strategies people use to respond to questionnaires like the PANAS. When subjects are asked to make global inferences about the affective dispositions that are extended in time, they are not veridical integrators of the momentary affective states that unfolded over the period in question. Rather, as a number of commentators have forcefully argued, they exhibit systematic heuristic biases that reflect the information that is accessible at the time (see Kahneman 1999; Schwarz and Strack 1999). In particular, in a series of elegant studies, Kahneman (1999) has demonstrated that individuals tend to adopt what he refers to as the "peak-end" rule for forming these retrospective affective evaluations. Thus, although an individual might be asked to rate how "nervous" he was during the past month, he is likely to weight excessively information about the peak episode of nervousness during this period, as well as his level of nervousness very recently. The peak intensity of the emotion in question may be especially related to amygdala activation, because it is likely to represent a response to a particularly threatening or novel episode. Such complexities in measuring subjective aspects of emotion underscores the need to develop more objective measures that do not depend on self-report and that can better capture the time course of emotional responding or what Davidson (1998a) has referred to as affective chronometry.

The fact that there exist reliable individual differences in baseline metabolic rate in the amygdala also requires comment in light of the earlier discussion about the amygdala's role in phasic affective processes. There is clearly intrinsic neural activity in the amygdala, even during sleep (Maquet et al 1996). As a number of studies have now shown, baseline nontask ("resting") levels of activation in the amygdala are associated with dispositional negative affect (Abercrombie et al 1998) and depression (Drevets et al 1992). Whether these baseline differences in amygdala activation reflect activation in response to the PET environment or whether such differences predict the magnitude of task-induced activation in the amygdala in response to emotion elicitors are questions that must be addressed in future research. We believe that when PET is used to measure baseline differences in amygdala activation, at least for the right amygdala, it likely reflects an important influence of the experimental situation itself. This claim is made on the basis of the fact that our recent evidence (Schaefer et al 2000) using MR-coregistration to extract glucose metabolic rate in several subcortical regions revealed that test–retest reliability over a 6-month period is excellent for all subcortical regions we examined (hippocampus, caudate, thalamus, left amygdala) except for the right amygdala. These findings are consistent with the idea that situational influences are important in modulating activation in the right amygdala.

Implications and Conclusions

On the basis of findings from several new studies reviewed above, we have suggested (Davidson 2000b) that at least one important component of what the ventromedial and/or orbital prefrontal cortex "does" in affective responding is modulate the time course of emotional responding, particularly recovery time. There are several facts critical to making this claim. First, there are extensive reciprocal connections between amygdala and PFC, particularly the medial and orbital zones of prefrontal cortex (Amaral et al 1992). The glutamatergic efferents from PFC likely synapse on γ-aminobutyric acid neurons (Amaral et al 1992) and thus provide an important inhibitory input to the amygdala. Second, LeDoux and his colleagues (Morgan et al 1993; but see Gewirtz et al 1997) demonstrated in rats that lesions of medial prefrontal cortex dramatically prolong the maintenance of a conditioned aversive response. These findings imply that the medial PFC normally inhibits the amygdala as an active component of extinction. In the absence of this normal inhibitory input, the amygdala remains unchecked and continues to maintain the learned aversive response. Other work on shifts in behavior following reward devaluation also underscore the importance of interaction between the amygdala and orbital PFC (Baxter et al 2000). Third are the data cited above indicating that individual differences in prefrontal activation asymmetry significantly predict the magnitude of the poststimulus startle following removal of the variance attributable to startle magnitude during the presentation of the emotional picture. In particular, left prefrontal activation appears to facilitate two processes simultaneously: 1) it maintains representations of behavioral-reinforcement contingencies in working memory (Thorpe et al 1983); and 2) it inhibits the amygdala. In this way, the time course of negative affect is shortened while the time course of positive affect is accentuated. And finally, findings using PET indicate that in normal subjects, glucose metabolism in left medial and lateral PFC is reciprocally associated with glucose metabolic rate in the amygdala (Abercrombie et al 1996). Thus, subjects with greater relative right-sided sided prefrontal

metabolism have higher metabolic activity in their amygdala. These findings are consistent with the lesion study of LeDoux and colleagues and imply that prefrontal cortex plays an important role in modulating activity in the amygdala. Increased activation in both right prefrontal and amygdala regions have been reported for several types of anxiety disorders, and the increase in amygdala activation that has been reported in depressed patients may be associated primarily with anxiety symptoms that are often found to be co-morbidly associated with depression.

Data were also presented that indicate individual differences in both tonic glucose metabolism and phasic activation in response to aversive stimuli in the amygdala. These individual differences predict dispositional negative affect. Whatever modulatory influence the prefrontal cortex might have over the amygdala, it appears that the magnitude of phasic activation of the amygdala by aversive stimuli accounts for a substantial portion of variance in self-reported dispositional negative affect, considerably more than any of our measures of prefrontal function. Thus, the proximal control of dispositional negative affect is likely to be more closely associated with amygdala function than with prefrontal function.

In light of the contributions of various sectors of the PFC and amygdala to affective style, is there specificity of this part of the circuitry for anxiety per se? And how are we to understand the many ways in which anxiety is expressed and the specific types of anxiety disorders that have been described? These are questions to which firm answers are not yet available; however, based on the extant literature, it is fair to say that there may be certain elements that are common across anxiety disorders that may be reflected in common neural substrates. For example, increased vigilance toward threat-related stimuli that have the capacity to stop ongoing behavior and re-orient processing capacity to address a perceived threat may be somehow generic to many anxiety disorders and may be reflected in tonically elevated activation of certain sectors of the right PFC, as Rauch and colleagues (Rauch et al 1997) have demonstrated across several different anxiety disorders. The specific stimuli that have the capacity to elicit increase in right-sided PFC and amygdala activation may vary as a function of learning; however, once these associations become learned, the cascade of central changes the learned cues produce may be similar across different anxiety disorders. Having argued for an invariant core that may be associated with some aspects of anxiety-related symptomatology, it is also important to highlight the likelihood that there will be some specificities as well, though the details of such specificity are not yet known.

A related issue concerns the extent to which the central mechanisms featured in this review are characteristic of normal anxiety, anxiety disorders, or both and whether the individual differences in anxiety-related affective styles are on a continuum. The research on individual differences in prefrontal and amygdala function implies that these individual differences are indeed on a continuum and suggests that the boundary between normal and pathologic variation is arbitrary. There may well be common genetic mechanisms associated with individual differences in the propensity toward anxiety-related affective processing along a broad continuum of variation; however, this issue has not yet been subjected to rigorous testing, and a more definitive resolution of this issue will require additional research.

The questions that are featured in this review are more tractable now than ever before. With the advent of echoplanar methods for rapid fMRI, sufficient data can be collected within individuals to examine functional connections among regions hypothesized to constitute important elements of the approach and withdrawal circuits discussed above. Individual differences in different aspects of these systems can then be studied with greater precision. Functional MRI methods also lend themselves to address questions related to affective chronometry (Menon and Kim 1999). In particular, we can calculate the slope of MR signal intensity declines following the offset of an aversive stimulus to provide an index of the rapidity of recovery from activation in select brain regions. Methods of PET using new radioligands that permit quantification of receptor density for specific neurotransmitters in different brain regions is yielding new insights directly relevant to questions about affective style (see e.g., Farde et al 1997). Traitlike differences in affective style are likely reflected in relatively stable differences in characteristics of the underlying neurochemical systems. Using PET to examine such individual differences promises to provide important syntheses between neurochemical and neuroanatomical approaches to understanding the biological bases of affective style.

Affective neuroscience (Davidson and Sutton 1995) seeks to understand the underlying proximal neural substrates of elementary constituents of emotional processing. In this article, I have provided a review of the role of the PFC and amygdala in approach and withdrawal motivational/emotional systems and illustrated the many varieties of individual differences that might occur in these systems, particularly as they relate to vulnerability to anxiety disorders. Research on prefrontal asymmetries associated with affective style was used to illustrate the potential promise of some initial approaches to the study of these questions. Modern neuroimaging methods used in conjunction with theoretically sophisticated models of emotion and psychopathology offer great promise in advancing our understanding of the basic mechanisms giving rise to affective style and affective and anxiety disorders.

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