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The neural circuitry of emotion and affective style: prefrontal cortex and amygdala contributions

Abstract. *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 orbitofrontal 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 affective style. Emphasis is placed upon affective chronometry, or the time course of emotional responding, as a key attribute of emotion that varies across individuals and is regulated by this circuitry.*

Key words. *Affective neuroscience – Affective style – Amygdala – Emotion regulation – Prefrontal cortex*

I. Introduction

Biobehavioral scientists are increasingly recognizing the importance of affective processes for the fundamental tasks of survival and

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adaptation (Damasio, 1994; Ekman and Davidson, 1994; Pinker, 1997). Affect modulates memory, facilitates decision-making, influences learning and provides the motivation for critical action in the face of environmental incentives. Affective processes also underlie individual differences in personality and temperament. Affect is a key component that governs risk for psychopathology (see Davidson et al., 1999a). In this article, evidence on the role of the prefrontal cortex and amygdala as key structures in circuitry that governs positive and negative affect and affective style will be reviewed.

II. 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; Schneirla, 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 formulations. 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 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. The focus will be on two key components of this circuitry – the prefrontal cortex (PFC) and the amygdala. For more extensive discussion of this entire circuitry, including other regions not considered here, see Davidson and Irwin (1999a) and Davidson et al. (2000c).

A large corpus of data at both the animal and human levels implicates various sectors of the PFC in emotion. The PFC is not

a zone of homogeneous tissue but rather has been differentiated on the basis of both cytoarchitectonic and 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 importance of functional asymmetries for different aspects of emotion in the prefrontal cortex 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 region participates in aspects of positive affect and when damaged leads to hedonic deficits, 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 (see 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., 1990a) while 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, in the next section a body of evidence will be reviewed 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, while the production of positive affect was associated with a pattern of predominantly left-sided metabolic increases in the pre- and post-central gyri. Using PET to measure regional cerebral blood flow, Hugdahl and his colleagues (Hugdahl et al., 1995; Hugdahl, 1998) 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, prior to 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 controls. 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 and colleagues (Davidson et al., 2000b), 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., 1998) have reported that patients with bilateral lesions of the ventromedial PFC 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 controls, while controls exhibit such autonomic change before they can consciously verbalize 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 and because of the negativity bias (see Cacioppo and Gardner, 1999; Taylor, 1991). This latter phenomenon refers to the general tendency of organisms to react more strongly to negative than to positive stimuli, perhaps as a consequence of evolutionary pressures to avoid harm. The findings from Bechara et al. (1999) on the effects of ventromedial PFC lesions on the anticipation of future positive *and* negative affective consequences are based upon 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 impairs an individual's capacity to anticipate future affective outcomes and consequently results 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 maintenance 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, while the former sector is most directly involved in the representation of goal states toward which these more elementary positive and negative states are directed.

The representation of affect in the absence of immediate cues for its elicitation is part of a more general process of emotion regulation that also likely critically depends upon the PFC (see Davidson et al., 2000c for an extensive discussion of this issue). Davidson et al. (2000c) suggested that the PFC plays a crucial role in the suppression of a negative affective state via an inhibitory connection from regions of the PFC, probably the orbital frontal cortex, to the amygdala.

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). Since 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 of where the learned information is stored is still a matter of some controversy (see Cahill et al., 1999; Fanselow 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 non-human 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., forthcoming; 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.

While 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., 1996; 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 controls 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., 1996; Morris et al., 1996; Phillips et al., 1997). In the Breiter et al. (1996) 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). The role of individual differences in amygdala activation in affective style will be addressed 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 the precise role it plays 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, while angry faces convey a threat but the source of the threat is unambiguous. A complicating factor in the interpretation of the data on neural responses to facial expressions is the nature of the experimental stimuli used in these studies. The studies that have been performed to date on the impact of different facial expressions of emotion have used the Ekman and Friesen (1976) set of facial affect pictures. The negative emotional faces used in this set are posed expressions. There is some evidence to suggest that full-blown fear faces of the sort that are illustrated in this set are quite unlikely to occur very frequently in real life (see Davidson, 1992). Therefore, as in studies of verbal learning and word recognition, there is a face frequency effect that may be operating here and the increased amygdala activation to the fear faces may, at least in part, arise as a consequence of their relative infrequency. In the domain of vocal expression, some findings indicate that bilateral destruction of the amygdala impairs the recognition of both fear and anger signals (Scott et al., 1997) while other findings suggest that the vocal recognition impairment

is more specific to fear (Sprengelmeyer et al., 1999). In intact subjects studied with fMRI fearful vocalizations were associated with a decrease in the MR signal from the right amygdala (Morris et al., 1999).

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). Other data indicate that conditioned aversive stimuli that are masked elicit right-sided amygdala activation while the same stimuli presented in an unmasked condition elicit left-sided amygdala activation (Morris et al., 1998). There are data at the rodent level that suggest that there might be important functional differences between left and 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 negative affect or whether it is specifically involved in only the initial acquisition of aversive 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., forthcoming) 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 a fearful endophenotype including

right prefrontal EEG activation or 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.

III. 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 physiological 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) and only highlights will be presented here. Using measures of scalp-recorded brain electrical activity, we found that indices of activation asymmetry based upon power spectral measures were stable over time and exhibited excellent internal consistency reliability (Tomarken et al., 1992b) thus fulfilling a number of important psychometric criteria for an index of a trait-like 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 very 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. These issues will be addressed in more detail later in the article.

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 controls (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 controls 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 types of behavior and biology comparable to what we observe in humans. We (Kalin et al., 1998) found that animals with greater relative right-sided prefrontal activation exhibit higher basal levels of the stress hormone cortisol and have higher cerebrospinal fluid levels of corticotropin-releasing hormone (Kalin et al., 2000), the molecule that initiates the cascade that begins with release of ACTH which then stimulates the release of cortisol. Similar data on relations between right-sided frontal EEG activation and cortisol have recently been reported in humans (Buss et al., 1997).

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 Snyder, 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 mostly a function of significant methodological limitations. 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. Davidson and Irwin (1999a) comment on the complexity of performing these analyses. Since 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. Using formal methods for assessing asymmetry, we found that MR activation differences in regions of the prefrontal cortex did predict

dispositional negative emotion. Individuals with greater right- compared with left-sided MR signal change in response to negative compared with neutral pictures reported more dispositional negative affect (see Davidson and Irwin, 1999a). These findings are consistent with those using brain electrical activity measures (e.g. Tomarken et al., 1992b).

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 post-negative-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 controls (Morgan et al., 1993; but see Gewirtz et al., 1997). Very recent data indicate that lesions in this region of prefrontal cortex particularly affect the retention of extinction after a long delay (Quirk et al., 2000). These data together 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. While immediate extinction is observed following lesions to this region, the consolidation of extinction appears to be disrupted after damage to this area (Quirk et al., 2000). 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 increased left prefrontal metabolic rate

have decreased metabolic rate in the amygdala (Abercrombie et al., 1996). We propose that this mechanism may be responsible for the dampening of negative affect and the shortening of its time course in those individuals who appear to be more resilient. Such an affective style may also facilitate the maintenance of approach-related positive affect.

The two key features of the circuitry underlying positive and negative affect highlighted in this article are the prefrontal cortex and the amygdala. In the section above, we detailed studies on the basic function of the amygdala in affective behavior. Here we ask the question 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 co-registered 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 – see Watson et al., 1988) in a group of depressed patients. Using the same measure of negative affect, we 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 ($r = .61$) (Davidson and Irwin, 1999a). 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 three 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 classical 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 than 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 pre-existing 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 amygdala 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 pre-existing 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 since it is likely to

represent a response to a particularly threatening or novel episode. Recent findings on the subjective reactions (assessed by questionnaire) of a patient with bilateral amygdala damage to potentially fearful stimuli are consistent with this notion (Sprengelmeyer et al., 1999). Such complexities in measuring subjective aspects of emotion underscore the need to develop more objective measures that do not depend upon self-report and 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 non-task (''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 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.

IV. Implications and conclusions

On the basis of findings from several new studies reviewed above, we have suggested that at least one important component of what 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 GABA neurons (Amaral et al., 1992) and thus provide an important inhibitory input to the amygdala. Second, LeDoux and others (Morgan et al., 1993; Quirk et al., 2000) 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. Third are the data cited in section III above indicating that individual differences in prefrontal activation asymmetry significantly predict the magnitude of the post-stimulus 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 from my laboratory indicate that in normal subjects glucose metabolism in left medial and lateral prefrontal cortex is reciprocally associated with glucose metabolic rate in the amygdala (Abercrombie et al., 1996). Thus, subjects with greater left-sided prefrontal metabolism have lower 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. At the same time, the left prefrontal cortex is also likely to play a role in the maintenance of reinforcement-related behavioral approach. Perhaps the damping of negative affect and shortening of its time course facilitate the maintenance of approach-related positive affect.

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.

Affective neuroscience is now flourishing, with extensive interaction between basic scientists working at the molecular level in animals and systems neuroscientists working at an integrative level in humans. By combining careful behavioral and peripheral psychophysiological measures with neuroimaging methods, we can track the dynamic unfolding of affect in time and trace the underlying neural substrates of the various subcomponents that comprise an emotional response. Using these combined methods, we can also begin to parse the domain of affective style in ways that better reflect how the brain works and that honor distinctions made by our neural architecture.

Of particular importance in the future will be the phenomena of affective plasticity – the plasticity of the neural circuitry associated with emotion. Relevant findings from the animal literature that are most pertinent to understanding such plasticity at the human level have been reviewed in Davidson et al. (2000a). Affective traits may be more akin to skills that are learnable than we have previously considered. Systematic training, particularly when it begins early in life, is likely to have demonstrable effects on the neutral circuitry of emotion and can potentially be exploited for the development of therapeutic interventions for the treatment of disorders of emotion. The science of emotion is likely to look very different a decade from now than it looks today.

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