

Emotion, Plasticity, Context, and Regulation: Perspectives From Affective Neuroscience

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The authors present an overview of the neural bases of emotion. They underscore the role of the prefrontal cortex (PFC) and amygdala in 2 broad approach- and withdrawal-related emotion systems. Components and measures of affective style are identified. Emphasis is given to affective chronometry and a role for the PFC in this process is proposed. Plasticity in the central circuitry of emotion is considered, and implications of data showing experience-induced changes in the hippocampus for understanding psychopathology and stress-related symptoms are discussed. Two key forms of affective plasticity are described—context and regulation. A role for the hippocampus in context-dependent normal and dysfunctional emotional responding is proposed. Finally, implications of these data for understanding the impact on neural circuitry of interventions to promote positive affect and on mechanisms that govern health and disease are considered.

Biobehavioral scientists are increasingly recognizing the importance of emotion for the fundamental tasks of survival and adaptation (A. R. Damasio, 1994; Ekman & Davidson, 1994; Pinker, 1997). Emotion facilitates decision making, has significant influence on learning and memory, 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 (see Davidson, Abercrombie, Nitschke, & Putnam, 1999). Some of the most impressive evidence for brain plasticity is emotional learning (LeDoux, 1996). Plasticity in the neural circuitry underlying emotion is also likely to play an important role in understanding the impact of early environmental factors in influencing later individual differences and risk for psychopathology (Meaney et al., 1996). Moreover, plasticity in the neural circuitry underlying emotion can be recruited for therapeutic

change using both nonpharmacological and pharmacological intervention (Davidson, 1994a).

In this article, we provide a broad overview of the underlying biological bases of emotion with a focus on the neural circuitry at the human level. We begin with some historical background to set the stage for modern psychophysiological and neuroscientific research. The subcomponents of emotion that are suggested by these findings are highlighted. Individual differences in affective style are then considered. The different parameters of affective style that can be objectively measured are identified, and some data are reviewed to illustrate how these parameters can be assessed. Plasticity in this circuitry is then described, and the implications of these data for understanding the etiology of psychopathology and stress-related symptoms are discussed. We then focus upon two key components involved in the determination of affective style and its plasticity-regulation and context. These terms are unpacked, and several varieties of regulation are delineated. The role of context and the neural substrates underlying context-dependent emotional responding are described. Dysfunctions in context regulation and their import for understanding certain forms of psychopathology are considered. Finally, several issues in this research area that will be important for the future are highlighted.

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Historical Background

Modern theoretical and experimental interest in the psychology and biology of emotion may be properly said to have begun with the American psychologist and philosopher William James. James's theories of the physiological antecedents and underpinnings of emotional experience have influenced psychologists through the present day, and these theories are still debated in the scientific literature. In his *Principles of Psychology*, James (1890/1981) repeated verbatim from an earlier publication what has become known as the James–Lange theory of emotion. James suggested that “bodily changes follow directly the perception of the exciting fact, and that our feeling of the same changes as they

occur IS the emotion" (p. 1065, emphasis in original).¹ James's theoretical account of the nature of emotion experience contains two important components that can be tested empirically. First, the physiological response to a stimulus is antecedent to the emotional experience (the felt emotion); more properly, the physiological response (sensation followed by motor output) in fact provides the basis for the emotional experience. Without this physiological component, there is no emotion. As we shall see, this idea has altered the course of emotion research in this century, leading to a search for autonomic states specific to different emotions. James's second premise, also stated unequivocally in the *Principles*, is that there are no brain centers or circuits, other than the necessary sensory and motor cortical areas, specifically involved in the experience of emotion. A major weakness of this theory is the failure to provide an account of why certain events trigger emotion-relevant peripheral changes whereas other events do not.

The idea that there are no dedicated brain centers for emotion was later questioned by Walter Cannon (1927, 1929). Cannon's criticisms were many, but the most salient may have been that the internal organs implicated by James and Lange in physiological reactivity are ill suited to perform the kinds of tasks that the James-Lange theory requires of them. Visceral organs are incapable of providing the complex information that would be necessary for fine distinctions in emotional experience, they are largely nonspecific in response to different kinds of stimuli, and they are too slow to account for rapid changes in emotional experience. Two experimental refutations of the James-Lange theory were presented by Cannon. First, stimulation of the viscera does not necessarily lead to qualitative changes in emotional state. Second, surgical separation of the viscera from the central nervous system does not alter emotional behavior. This latter criticism was grounded on experiments performed by Cannon and Phillip Bard in which the "sham rage" response was observed in decorticate animals (Bard, 1928, 1929). On the basis of further experimentation and the extant lesion literature, Bard made a case for a neural circuit underlying the autonomic nervous system (ANS) responses seen in sham rage involving the caudal hypothalamus and caudoventral thalamus. Sham rage was characterized as a disinhibition syndrome, with the removal of inhibitory cortex leading to the striking autonomic and behavioral changes seen in these animals (Bard & Mountcastle, 1948). In terms of the present discussion, perhaps the most important aspect of Cannon and Bard's work is the experimental elucidation of specific neural circuits involved in the expression (and presumably, the experience) of emotion, in direct opposition to James's notion that there are no specific neural centers of emotion. The importance of this idea cannot be overestimated, although several of Cannon's specific criticisms of the James-Lange hypothesis have since been disproved.

The Cannon-Bard hypothesis of the involvement of diencephalic structures in emotion expression and of cortical structures in emotion experience sparked other researchers to posit more specific and elaborate neural circuits of emotion. The work of Papez has been particularly influential in this regard (see LeDoux, 1987, for a thorough review). Papez theorized that the functions of central emotion are instantiated in a complex circuit involving the hypothalamus, anterior thalamic nucleus, hippocampus, and cingulate cortex (Papez, 1937). The hypothalamus was thought to be the structure that imbued incoming stimuli with emotional significance, whereas the cingulate cortex was thought to be involved in

the experience of emotion. More recently, MacLean (1949, 1952) argued that the hippocampal formation (a term that included the amygdala, an important structure that has figured prominently in many modern-day theories of emotion) plays a paramount role in emotional experience. MacLean classified brain structures by putative evolutionary stage: reptilian (essentially, brain stem and cerebellum), paleomammalian, and neomammalian. The paleomammalian brain, dubbed by MacLean the limbic system, includes the septum, amygdala, hypothalamus, anterior thalamic nucleus, tegmentum, hippocampus, and insular cortex (MacLean, 1952, 1993). Although, as pointed out by LeDoux (1987), the concept of a unified limbic system is undoubtedly a convenient but imprecise shorthand for researchers, it has had an enduring influence in their attempt to better characterize the neural circuits involved in emotional experience and expression. The effect of the theories of Papez and MacLean on subsequent emotion research has been overwhelming. Although many of the specific tenets of these early emotion theories have since proved unsupportable, they have had the salutary effect of spurring researchers to search for the specific and complex neural circuitry involved in emotion. However, before turning our attention to more recent theoretical models underscoring the importance of central nervous system activity in emotion, we examine the experimental legacy prompted by the ideas of William James. Beginning in the middle part of this century, this legacy took the forms of a search for autonomic specificity associated with different emotional states and an ongoing discussion concerning the importance of facial feedback in emotion experience.

As reviewed above, early experimental work led Cannon to discount James's ideas about physiological antecedence in emotional processes. In an attempt to test James's hypotheses, later researchers attempted at least to show physiological specificity for different emotional states. In a perhaps unwarranted narrowing of James's notions (Ellsworth, 1994), this research has generally taken the form of a search for autonomic specificity. There is some evidence to support the notion of such specificity, at least for some negative emotions such as fear and anger (see, e.g., Ax, 1953; Schachter, 1957), though this issue has become one of the more contentious ones among emotion researchers, as is elaborated below. Schachter and Singer's (1962) now famous article reported the results from several experimental manipulations designed to assess the relative contributions of bodily feedback and cognitive appraisal to the determination of emotional state. The authors hypothesized that participants would label their emotional state following an epinephrine injection according to available cognitions provided by the context manipulated by the experimenter. They found this to be the case: Participants who were either uninformed or misinformed about the effects of the injections tended to feel (according to self-report) and behave similarly to confederates who acted angry or euphoric, whereas participants who were correctly informed regarding the injection effects did not (Schachter & Singer, 1962). Subsequent emotion theorists have thus used the Schachter and Singer study as evidence for the nonspecificity of autonomic activity during emotion. This view holds that

¹ See Ellsworth (1994) for a view of this passage as an exaggerated and incomplete account of James's thoughts on emotion. Also see James (1894/1994) for a rebuttal of his contemporary critics.

emotion is accompanied by undifferentiated physiological arousal that is then attributed to whatever the most salient contextual cue might be. Arousal plus cognition are the two necessary ingredients that combine to form specific emotions. The specificity in this view is derived from the cognitions and not from the physiological change (for a review, see Leventhal & Tomarken, 1986).

However, Levenson (1992) has recently argued that the Schachter and Singer study was an invalid test of ANS differentiation because the study design used ANS activity as an independent variable (manipulated by epinephrine injection) rather than as a dependent variable. Levenson cited several studies employing various emotion elicitation techniques, all of which provide some support for ANS differentiation in emotion. In general, ANS differentiation has been found primarily for negative emotions. Heart rate acceleration has been seen in states of sadness, anger, and fear, whereas heart rate deceleration has been observed in states of disgust. This pattern of effects has been seen not only in Westerners but also in participants from the Minangkabau of West Sumatra, providing support to the hypothesis that some types of ANS specificity are not culturally specific (Levenson, Ekman, Heider, & Friesen, 1992).

Overall, there is good evidence for some ANS specificity, particularly for negative emotions, although not all findings have been supportive (cf. Cacioppo, Klein, Berntson, Hatfield, 1993; Leventhal & Tomarken, 1986). Stemmler (1989, 1992) has argued convincingly for the use of stricter constructs of ANS specificity in research of this type and for an increased recognition of the importance of situational variables in ANS activity during emotional states. According to Stemmler, findings of significantly different physiological profiles following the induction of qualitatively different emotional states in differing situational contexts are not sufficient for claiming physiological emotion specificity (Stemmler, 1992). Thus, the same emotion may lead to different physiological profiles depending on the situational variables within which the emotion is induced, and different emotions may be associated with the same physiological profiles in some instances. For example, Stemmler (1989) reported that real-life fear induction (listening to the conclusion of Poe's "The Fall of the House of Usher" in a darkened room, with appropriately spooky background music) led to a statistically different autonomic profile than did a fear imagery task in which participants were asked to recollect and speak about a frightening personal event.

Given the evidence reviewed above on ANS activity and emotion, what can be said about the role of ANS activity in emotion? The data certainly cannot support a primary role for autonomic patterning in the determination of emotional experience because reported emotional experience is far more differentiated than the autonomic changes that have been observed. Moreover, most investigators would agree that peripheral autonomic changes are simply too coarse to play a causal role in the determination of emotional experience. Rolls (1999) recently argued that "the peripheral changes produced during emotion are not sufficiently distinct to be able to carry the information which would enable one to have subtly different emotional feelings to the vast range of different stimuli that can produce different emotions" (pp. 71-72).

The ANS provides crucial support for action. It mobilizes the resources necessary for different action sequences, both in preparation for action and in action itself. It is likely that autonomic changes accompanying emotion provide important support for the

action sequelae recruited by emotion. On this view, a primary determinant of autonomic patterning is the nature of the action plan or pattern recruited by the emotion in question in that specific context (see Davidson, 1994b, for a more extended discussion of this issue). Some emotions may be associated with a broader range of action sequelae than others and as a result, may be associated with more variable patterns of autonomic discharge, particularly in experimental contexts where action is minimized.

Of particular note in the literature on autonomic correlates of emotion is the fact that no systematic, replicable differences that distinguish between positive and negative affect have been reported, despite the fact that this valence dimension is an extremely salient one and arises in every major conceptual scheme for the structure of emotion (see, e.g., Watson, Wiese, Vaidya, & Tellegen, 1999). For example, when pictures designed to elicit positive versus negative affect are compared, minimal ANS differences have been observed between these stimulus categories despite the fact that the emotion-modulated startle does reliably distinguish between them (Lang, 1995). In the domain of emotion, the most consistent correlate of autonomic discharge is the arousal or intensity dimension of emotion where many investigators have reported reliable relations between self-reports of affect intensity and magnitude of autonomic output, particularly skin conductance (Lang, Greenwald, Bradley, & Hamm, 1993). The association between the magnitude of electrodermal change and the intensity of emotional experience goes back many decades with many reports of it appearing in the 1930s and 1940s and is compellingly summarized by McCurdy (1950).

Following the pioneering work of Tomkins (1962), Ekman, Levenson, and Friesen (1983) developed the Directed Facial Action Task in which participants are provided with muscle-by-muscle instructions that constitute specific facial expressions associated with different emotions. Some of the most impressive evidence for autonomic specificity associated with different discrete emotions has been derived from this task (see, e.g., Levenson, Ekman, & Friesen, 1990). Although there is controversy about the factors responsible for the patterns of autonomic change associated with different expression types (see, e.g., Boiten, 1996), this work has been interpreted by some to provide support for the feedback ideas championed by James and subsequently by others. Because voluntarily producing certain facial poses recruits autonomic change, many investigators have assumed that such findings provide strong support for feedback theories (Strack, Martin, & Stepper, 1988). This logic holds that the autonomic changes are a consequence of the feedback from the facial musculature. Unfortunately, this is not a logical necessity as autonomic changes can presumably arise as a function of the efferent patterns of discharge associated with different facial productions. In other words, there might be central loops through which the production of facial poses can influence the neural circuitry of emotion and in turn, emotion-related information processing. (This alternative account is described more fully below.) Indeed, this is the general form of the explanation preferred by Ekman (1992), who posited a "central, hard-wired connection between the motor cortex and other areas of the brain involved in directing the physiological changes that occur during emotion" (p. 65).

There have been a flurry of reports largely in the social psychological literature showing effects of manipulating participants' faces in ways that putatively do not call attention to changes in

emotional expression (Laird et al., 1994; Strack et al., 1988). These studies have examined the impact of such facial manipulations on a variety of different dependent measures including measures of emotional reactivity, mood and mood-related cognition. Although these data are certainly consistent with the feedback ideas advanced originally by James, they fail to provide definitive support for this position. In particular, in these types of studies, participants must voluntarily maintain certain facial poses. To accomplish such a task, efferent commands to the facial muscles to assume a particular pose are required. It is entirely possible that the affective changes attributed to feedback from the periphery arise instead from central events. This alternative is treated in detail in subsequent sections.

If feedback from the periphery were necessary for differentiated emotional experience, blocking skeletal-muscular activity would eliminate emotion. There were several very early reports of animals and humans administered neuromuscular blocking agents, which produce paralysis of the peripheral musculature. Despite being unable to move their faces or other parts of their skeletal-musculature, curarized animals given discrete cortical stimulation displayed emotion-related autonomic changes that were comparable to those observed without curare (Hoff & Green, 1936); drug-induced paralysis also failed to affect autonomic aversive conditioning (Girden, 1943). Studying patients with spinal cord lesions to evaluate the role of peripheral feedback in emotion, Hohmann (1966) reported that such patients described their emotional feelings after their injury as being somewhat diminished in intensity, though overt emotional behavior continued unabated. However, in a more recent, larger, and more systematic study of such patients, Bermond, Nieuwenhuys, Fasotti, and Schuerman (1991) found that overall levels of emotional excitability actually increased rather than decreased following injury. These more recent observations again call into question a strong form of the feedback hypothesis that features peripheral feedback as necessary for the experience of emotion, though central views of human emotion were already receiving some attention in the early part of the century (see, e.g., Dana, 1921). It may however still be the case that feedback from the periphery plays a contributory role in modulating the intensity of emotional experience.

The effort to place the source of emotional differentiation in the periphery is reminiscent of a similar project in the cognitive domain. Investigators both in the early part of the century (Jacobson, 1930; Shaw, 1938) and more recently (McGuigan, 1966, 1997) have attempted to account for complex cognition as covert speech. By recording muscle activity from the periphery, particularly from the vocal apparatus, they hoped to detect signals that would correlate with specific thought content. It is noteworthy that these efforts, in both the cognitive and affective domains, were favored during a period in American psychology that was dominated by behaviorism. Placing the source of mental processes in the periphery was something that would be palatable to the behaviorism of the time. However, this project never really made much headway, though some limited association between peripheral muscular activity and various measures of thought was obtained (see McGuigan, 1966, for a review). Just a little later in this century, several neuropsychologists and neuroscientists began investigating the role of peripheral feedback in sensory and motor function and whether such feedback was necessary for complex sensory and motor functions (Taub, Ellman, & Berman, 1966;

Teuber, 1972). These investigations led to proposals about central feedforward mechanisms that provide the brain with "efferent copy" so that peripheral feedback is not required. The classic case for this was that described by Teuber for eye movements where the frontal eye fields were hypothesized to produce corollary discharge to visual regions of the brain that inform these areas of an impending eye movement. In this way, the visual world does not jump around with each eye movement but rather remains stable as a function of corollary discharge produced by the frontal eye fields. Other research by Taub demonstrated that peripheral feedback from the somatic musculature was not required for an animal to perform complex movements (Taub et al. 1966).

The upshot of this and related work has been to draw attention to the importance of the central nervous system and to put mentation back into the brain rather than postulating schemes that would enable it to remain in the periphery. LeDoux (1994), for example, has forcefully argued that the place to search for differentiation is in the brain rather than the periphery, though he acknowledged the potential role of peripheral feedback in modulating aspects of emotional intensity. Most of the remainder of this article is concerned with the examination of the central circuitry of emotion.

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 certain forms of positive and negative affect (Cacioppo & Gardner, 1999; Davidson & Irwin, 1999b; Gray, 1994; Lang, Bradley, & Cuthbert, 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 (1999b) 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. Note that not all negative emotions are classified as withdrawal-related. Anger is a case in point because it is often associated with approach behavior. Consistent with this conjecture are data that indicate that anger does not follow the usual pattern of right-sided prefrontal activation observed during withdrawal-related negative emotion (see, e.g., Fox & Davidson, 1988; Harmon-Jones & Allen, 1998). A variety of evidence indicates that the approach and withdrawal systems are implemented in partially separable circuits, and it is to this evidence that we now turn. Our focus is 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 (1999b).

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 homogeneous zone of tissue but rather has been differentiated on the basis of both cytoarchitectonic and functional considerations. The two major subdivisions of the primate PFC most pertinent to this discussion are the dorsolateral and orbitofrontal sectors. This latter sector overlaps considerably with the ventromedial PFC. These sectors of the PFC are distinguished primarily on the basis of projection zones from the dorsomedial nucleus of the thalamus. The magnocellular, medial portion of the dorsomedial nucleus projects to the orbital surface of the PFC (which includes Brodmann's areas 12 and 13). This sector of the PFC is typically referred to as the orbitofrontal cortex and has historically been closely linked with emotion. The parvocellular, lateral portion of the dorsomedial nucleus projects to the dorsolateral PFC, which has historically been assigned a primary role in short-term or working memory, though it is likely to also participate in aspects of emotional processing. 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 of patients with unilateral cortical damage (Gainotti, 1972; Robinson, Starr, & Price, 1984; Sackheim 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, likely including more than one sector of the PFC and often other brain regions as well. The general interpretation that has been placed on these studies is that depressive symptoms are increased following left-sided anterior PFC damage because this brain territory participates in a circuit 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 & Downhill, 1995, for a review), some inconsistencies have also appeared (see, e.g., Gainotti, Caltagirone, & Zoccolotti, 1993; House, Dennis, Mogridge, Hawton, & Warlow, 1990). Davidson (1993) has reviewed these studies in detail 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 & 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 should simply reflect a propensity but should 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, P. L. Morris, Robinson, Raphael, and Hopwood (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 approach-related positive and withdrawal-related negative affective states shift the asymmetry in prefrontal brain electrical activity in lawful ways. For example, film-induced disgust and fear increases relative right-sided prefrontal and anterior temporal activation (Davidson, Ekman, Saron, Senulis, & Friesen, 1990), whereas induced positive affect elicits an opposite pattern of asymmetric activation. Similar findings have been obtained by others (e.g., Ahern & Schwartz, 1985; Jones & Fox, 1992; Tucker, Stenslie, Roth, & Shearer, 1981). In addition, we 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 predict differences in dispositional affective style. Using an extended picture presentation paradigm designed to evoke longer duration changes in mood (Sutton, Davidson, Donzella, Irwin, & Dotts, 1997), we measured regional glucose metabolism with positron emission tomography (PET) to ascertain whether patterns of anterior asymmetry similar to those found using electrophysiological measures would be found using this very different and more precise method of assessing regional brain activity (Sutton, Ward, et al., 1997). During the production of negative affect, we observed right-sided increases in metabolic rate in anterior orbital, inferior frontal, middle, and superior frontal gyri; 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, 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, Marshall, Tomarken, and Henriques (2000), 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, Savage, Alpert, Fischman, and Jenike (1997) found two regions of the PFC that were consistently activated across groups: the right inferior PFC and the right medial orbital PFC.

The ventromedial PFC has been implicated in the anticipation of future positive and negative affective consequences. The case of Phineas Gage is probably the most well-known in both the neurological (Harlow, 1868) and popular (A. R. Damasio, 1994) literatures. Gage was injured when a tamping rod used to compress explosives for the purpose of creating rail passes through mountainous regions caused an explosion that sent the rod up through his cheekbone, into his orbitofrontal cortex and then out of his skull. Remarkably, he survived the accident, but as has now been well documented, his affective behavior and personality changed dramatically. He became quite impulsive and exhibited extreme

forms of emotional instability. More than 100 years later, using the preserved skull of Gage, H. Damasio and her colleagues (H. Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994) reconstructed Gage's brain volume and the path of the tamping rod. Using these image reconstruction methods, H. Damasio et al. were able to demonstrate that the injury Gage sustained was primarily in the orbitofrontal/ventromedial PFC. Shimamura (1999) reported on another case from the mid-1800s, that of the famous photographer and inventor Eadweard J. Muybridge. In the summer of 1860, Muybridge boarded a stage coach in San Francisco bound for St. Louis. In northeastern Texas, the driver of the coach lost control of the horses, and the coach sped down the side of a mountain and crashed. One man on board was killed, and all the others were injured. From a variety of evidence in the historical record, Shimamura concluded that Muybridge suffered from orbitofrontal damage. He showed many of the same affective and personality changes first described in Phineas Gage.

In the modern era, Damasio, Bechara, and colleagues have most systematically studied the emotional behavior of patients with damage to this sector of the PFC. For example, Bechara, Damasio, Damasio, and Anderson (1994) 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, whereas controls exhibit such autonomic change before they explicitly know that the choice is risky (Bechara, Damasio, Damasio, & Lee, 1999; Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Tranel, Damasio, & Damasio, 1996).

The findings from the lesion method when effects of small unilateral lesions are examined and from neuroimaging studies in normal participants 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.² Less evidence is available for the domain of positive affect because positive affect is much harder to elicit in the laboratory and because of the negativity bias (see Cacioppo & Gardner, 1999; Taylor, 1991). This latter phenomenon refers to the general tendency of organisms to react more strongly to negative compared with positive stimuli, perhaps as a consequence of evolutionary pressures to avoid harm. The findings from Bechara et al. (1994) 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 the PFC as well.

Systematic studies designed to disentangle the specific roles 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 (see, 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 individ-

ual'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 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. Note that our conception of affective working memory is different from Rolls's (1999) proposal that the orbitofrontal cortex plays a role in the maintenance of reinforcement associations. According to his proposal, synaptic modification occurs in the orbitofrontal cortex, which enables the organism to retain the reward value of a large number of stimuli. These associations can be stored for long periods of time and recalled whenever a learned stimulus is encountered again in the future. Our conception of affective working memory involves the maintenance of actual emotion during periods when emotional stimuli are no longer present. This process is conceptualized as playing a critical role in guiding behavior in the absence of immediately available incentives.

With regard to the different functional roles of the dorsolateral and ventromedial sectors of the PFC, Davidson and Irwin (1999b) 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. On the basis of mostly nonhuman primate neurophysiological data, Rolls (1999) has cogently argued that the orbitofrontal sector of the PFC implements rapid stimulus-reinforcer association learning and the correction of these associations when the contingencies of reinforcement change. Rolls has also marshaled considerable evidence to support the notion that the orbitofrontal cortex is the major zone that represents primary reinforcers. The animal literature has not systematically examined whether the representations of reward versus punishment reinforcers are differentially lateralized.

The Amygdala

A large corpus of research at the animal—mostly rodent—level has established the importance of the amygdala for emotional processes (see, e.g., Aggleton, 1993; Cahill & McGaugh, 1998; LeDoux, 1996). Because many reviews of the animal literature have appeared recently, a detailed description of these studies is not presented here. LeDoux (1993) and his colleagues have mar-

² It should be noted that the assessment of asymmetric activations in neuroimaging studies has typically not been rigorously performed. Most image analysis methods reveal voxels of significant activation when comparing between two conditions and/or groups. If an activation reaches statistical threshold in one hemisphere but fails to reach threshold in the opposite hemisphere, it is considered asymmetric. However, the proper test of an asymmetric effect is through a formal evaluation of the Condition (or Group) $\times$ Hemisphere interaction. Many of the effects that have been reported as asymmetric in the literature probably would not survive such an interaction test. See Davidson and Irwin (1999a, 1999b) for a more detailed discussion of this issue.

shaped 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 are still matters of some controversy (see Cahill, Weinberger, Roozendaal, & McGaugh, 1999; Fanselow & LeDoux, 1999). Also not resolved is the extent to which the amygdala participates in the learning of both negative and positive stimulus–incentive associations, as well as whether there are functional differences between the left and right amygdala (Davidson & Irwin, 1999b). 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, as well as 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 that preserve fibers of passage are made, nothing resembling the Kluver–Bucy syndrome is observed (Kalin, Shelton, & Davidson, 2000). 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 than is apparent from the animal evidence.

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, Damasio, Tranel, & Damasio, 1996; Adolphs, Tranel, Damasio, & Damasio, 1995; 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 participants 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 controls (Adolphs, Tranel, & Damasio, 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 (i.e., the perception of emotional cues in contrast to the production of emotion) 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 participants, 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 (see, e.g., Breiter, Rauch, et al., 1996; Rauch, van der Kolk, Fislis, & Alpert, 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, Etcoff, et al., 1996; P. L. Morris et al., 1996; Phillips et al., 1997). In the Breiter, Etcoff, 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, Morris, Dolan, & Friston, 1998; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; J. S. Morris, Ohman, & Dolan, 1998). Amygdala activation in response to several other experimental procedures for inducing negative affect, including unsolvable anagrams of the sort used to induce learned helplessness (Schneider et al., 1996), aversive olfactory cues (Zald & Pardo, 1997), and aversive gustatory stimuli (Zald, Lee, Fluegel, & Pardo, 1998), has been reported. Other data on individual differences in amygdala activation and their relation to affective style are treated in the next section.

The findings on the role of the amygdala in affective processes from both the lesion studies and neuroimaging raise a number of important questions about the functional significance of amygdala activation and the 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, though it is also the case that most laboratory-induced negative affect is more intense than positive affect, despite considerable efforts to insure that they are matched.³ In a study of the effects of cocaine on cocaine addicts, Breiter et al. (1997) reported significant deactivation in the amygdala during self-

³ Davidson et al. (1990) have offered a set of methodological desiderata for physiological studies of emotion. Included among these is the necessity of matching the intensities of positive and negative affect so that any differences found between them can be attributed to valence and not simply to intensity. Although many investigators recognize the need for this control, it is often difficult to implement and to verify.

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 expressions, 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 whose source 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 expressions (Scott et al., 1997) are not.

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 have reported changes in activation in the left amygdala (see, e.g., Schneider et al., 1997), some have reported changes in the right amygdala (see, e.g., Rauch et al., 1996), and some have reported bilateral changes (see, e.g., Irwin et al., 1996). There are data at the rodent level that suggest that there might be important functional differences between left versus right amygdala lesions (Coleman-Meschers & 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 Condition $\times$ Hemisphere interaction. Virtually none of the studies in the human neuroimaging literature have performed this crucial test (see Davidson & Irwin, 1999a, 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., 2000) have recently performed studies in Rhesus monkeys tested before and after very discrete excitotoxic lesions of the amygdala that preserve fibers of passage and destroy only cell bodies. Complete destruction of the amygdala in these animals resulted in a dramatic attenuation of behavioral signs of fear in response to a snake. However, such lesions did not have any noticeable impact on freezing in response to a human intruder paradigm (see Kalin & Shelton, 1989), nor did the lesions affect any of the biological correlates that have been found to be associated with an anxious endophenotype, including right prefrontal electroencephalographic (EEG) activation or baseline cortisol (Kalin, Larson, Shelton, & Davidson, 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 by using startle magnitude, fMRI signal change in the amygdala, or ratings on a self-report scale. Each of these obviously reflects activity in very different systems, and activation in these systems does 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. Virtually nothing is known 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, Ruffalo, Nietert, & Davidson, 2000; Tomarken, Davidson, Wheeler, & Kinney, 1992), though this information is crucial if researchers 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 2 decades of previous research, we have performed a large number of studies designed to examine the role of activation asymmetries in the PFC and other anterior cortical zones in aspects of affective style. This work has been reviewed recently (Davidson, 1995, 1998a), and only highlights are 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 exhibited excellent internal consistency reliability (Tomarken, Davidson, Wheeler, & Kinney, 1992), thus fulfilling a number of important psychometric criteria for an index of a traitlike construct. In a series of studies, we found that there were large individual differences in the magnitude and direction of baseline asymmetric activation in brain electrical activity measures obtained from prefrontal scalp regions⁴ in both infants (Davidson & Fox, 1989) and adults (Davidson & 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

⁴ It is important to note that in referring to the brain electrical activity findings, we state that we are examining activity from prefrontal scalp regions. When using measures of brain electrical activity, definitive inferences about the sources of the scalp-recorded surface potentials are difficult to make. Thus, we qualify our descriptions by noting that such measures reflect scalp topography. Whether the scalp topographic differences actually reflect different underlying sources must be addressed in future research with simultaneous measures of both brain electrical activity and either blood flow or metabolism (see Larson et al., 1998, for a recent example).

compared with their left-activated counterparts (Davidson & 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 & Rickman, 1999). In adults, we have found that individual differences in such measures predict dispositional mood (Tomarken, Davidson, Wheeler, & Doss, 1992), self-report measures of behavioral activation and inhibition (Sutton & Davidson, 1997), repressive defensiveness (Tomarken & Davidson, 1994), reactivity to positive and negative emotion elicitors (Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993), baseline immune function (Kang et al., 1991), and reactivity of the immune system to emotional challenge (Davidson, Coe, Dolski, & Donzella, 1999). In very recent work (Larson, Sutton, & Davidson, 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 PFC may play a role in the regulation of the time course of emotional responding and/or in the active inhibition of negative affect. We return to these issues 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 found that depressed subjects and individuals who were currently euthymic but had a history of past depression exhibited less left prefrontal activation compared with never-depressed controls (Henriques & Davidson, 1990, 1991). We also found that when social phobics anticipated making a public speech, they showed large increases in right-sided prefrontal activation though they did not differ from controls at baseline (Davidson et al., 2000).

In a series of studies with Kalin (Davidson, Kalin, & Shelton, 1992, 1993; Kalin, Larson, et al., 1998), we have demonstrated that similar activation asymmetries could be measured in Rhesus monkeys and that they predicted types of behavior and biology comparable to those we observed in humans. In the most recent effort of this kind, we (Kalin, Larson, et al., 1998) found that animals with greater relative right-sided prefrontal activation exhibited higher basal levels of the stress hormone cortisol. Similar data have recently been reported in humans (Buss, Dolski, Malmstadt, Davidson, & Goldsmith, 1997).

A number of our original EEG observations have now been independently replicated by others (Ahern & Schwartz, 1985; Allen, Iacono, Depue, & Arbisi, 1993; Dawson, Klinger, Panagiotides, Hill, & Spieker, 1992; Fox, 1991; Harmon-Jones & Allen, 1997; Jacobs & Synder, 1996; Wiedemann et al., 1999), though a few studies reporting only partial replications of aspects of our original findings have appeared (Hagemann, Naumann, Becker, Maier, & Bartussek, 1998; Reid, Duke, & Allen, 1998). Davidson (1998b) has called attention to a number of crucial methodological and conceptual issues in these replication attempts and suggested 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, 1999b), only a very small handful of studies using PET or fMRI have conducted the proper statistical comparison to uncover asymmetry effects in their data. Irwin et al. (2000) commented 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. Irwin et al., using formal methods for assessing asymmetry, found that fMRI activation differences in regions of the PFC did predict dispositional negative emotion. Individuals with greater right- compared with left-sided fMRI signal change in response to negative compared with neutral pictures reported more dispositional negative affect. These findings are consistent with those using brain electrical activity measures (see, e.g., Tomarken, Davidson, Wheeler, & Kinney, 1992).

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 that found that rats with lesions of the medial PFC showed dramatically slower extinction of a learned aversive response compared with sham-operated controls (Morgan, Romanski, & LeDoux, 1993; but see Gewirtz, Falls, & Davis, 1997). These findings imply that there is a descending pathway between the medial PFC and the amygdala (Amaral, Price, Pitkanen, & Carmichael, 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 PFC. Consistent with this idea, recent PET findings suggest that in normal human participants, glucose metabolism in the left medial and lateral PFC is reciprocally coupled to metabolic activity in the amygdala, such that those participants 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 PFC and the amygdala. In the section above, we detailed studies on the basic function of the amygdala in affective behavior. Here, we ask 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, one can draw regions of interest around the amygdala on an MRI 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-participant 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, Clark, & Tellegen, 1988) in a group of depressed patients (see Figure 1). Using the same measure of negative affect, we (Irwin, Anderle, Sutton, Kalin, & Davidson, 2000) have also found that fMRI 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 ($r = .63$; see Figure 2). 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, Fischer, Wik, Larsson, & Fredrikson, 1997) and fMRI (LaBar et al., 1998) reported that those participants 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

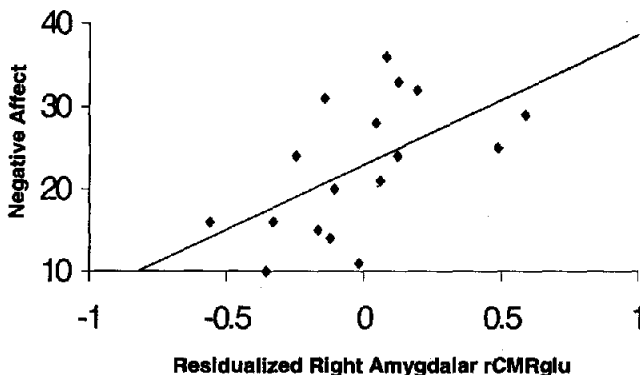


Figure 1. Scatter plot of the relation between dispositional negative affect in depressed patients assessed with the Positive and Negative Affect Schedule trait negative affect scale (Watson et al., 1988) and glucose metabolism in the right amygdala. rCMRglu refers to regional cerebral metabolic rate for glucose (assessed with MRI-coregistered regions of interest and position emission tomography), residualized for global metabolic rate. $N = 17$, $r = .56$, $p = .02$. From "Metabolic Rate in the Right Amygdala Predicts Negative Affect in Depressed Patients," by H. C. Abercrombie, S. M. Schaefer, C. L. Larson, T. R. Oakes, K. A. Lindgren, J. E. Holden, S. B. Perlman, P. A. Turski, D. D. Krahn, R. M. Bencs, and R. J. Davidson, 1998, *NeuroReport*, 9, p. 3505. Copyright 1996 by Lippincott Williams & Wilkins. Adapted with permission.

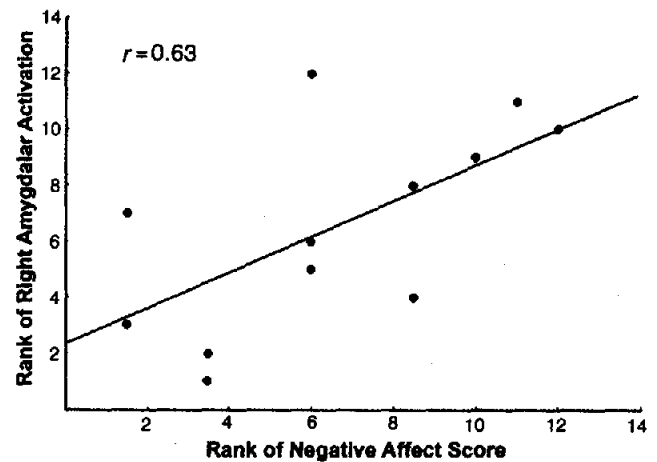


Figure 2. Scatter plot of the relation between dispositional negative affect in normal participants assessed with the Positive and Negative Affect Schedule trait negative affect scale (Watson et al., 1988) and fMRI signal change in the right amygdala in response to negative versus neutral pictures. $N = 12$. From "Activation of the Right Amygdala Detected With Functional MRI Predicts Dispositional Negative Affect," by W. Irwin, M. J. Anderle, S. K. Sutton, N. H. Kalin, and R. J. Davidson, 2000, manuscript in preparation. Copyright 2000 by W. Irwin. Adapted with permission.

response to the drug had significantly greater activation of the amygdala compared with those 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 participants with greater metabolic rate in the right amygdala reported higher levels of dispositional negative affect as assessed by the PANAS. A similar association was found using the identical affect measure with fMRI where participants showing larger fMRI signal increases in the amygdala in response to negative versus neutral pictures reported higher levels of dispositional negative affect. The PANAS requires participants 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 participants 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 & 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 underscore 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 MRI 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.

Plasticity in the Central Circuitry of Emotion

As we noted in the discussion of the central circuitry of emotion, the amygdala is clearly a site of plasticity in the brain. It is involved in emotional learning, whether or not it is itself the site of storage of new stimulus-threat associations. Recent work by LeDoux and his colleagues is beginning to characterize the molecular changes in the amygdala that accompany newly acquired aversive learning (Schafe, Nadel, Sullivan, Harris, & LeDoux, 1999; Weisskopf & LeDoux, 1999). These findings underscore the fact that although there are stable individual differences in activation patterns in the central circuitry of emotion, there is also pronounced plasticity in this circuitry. One of the major challenges for human affective neuroscience in the next century will be to better understand the environmental forces that shape the circuitry of emotion. Answers to this question will depend on the findings from longitudinal studies where sensitive measures of both brain function and

structure can be obtained along with measures of environmental change and behavioral measures of emotional reactivity.

For now, most of the extant data directly relevant to this issue is at the animal level. In a series of studies, Meaney and his colleagues (Caldji et al., 1998; Liu et al., 1997; Meaney, Aitken, van Berkel, Bhatnagar, & Sapolsky, 1988; see Francis & Meaney, 1999, for a recent review) have demonstrated that an early environmental manipulation in rats' frequency of maternal licking/grooming and arched-back nursing produces in the offspring a cascade of biological changes that shape the central circuitry of emotion and consequently alter the animal's behavioral and biological responsivity to stress. This work provides an elegant model for plasticity in this central circuitry and important clues for the study of similar influences at the human level. In particular, Meaney and his colleagues found that the adult offspring of high licking/grooming and arched-back nursing mothers displayed substantially reduced behavioral signs of fearfulness to novelty compared with the offspring of mothers low in these maternal characteristics. In addition, the offspring of mothers high in these traits showed increased central benzodiazepine receptor densities in various subnuclei of the amygdala as well as in the locus ceruleus (LC), increased α_2 adrenoreceptor density in the LC, and decreased corticotrophin releasing hormone (CRH) receptor density in the LC (Caldji et al., 1998). In other research, they found that rats exposed to high licking/grooming mothers exhibited a permanent increase in concentrations of receptors for glucocorticoids in both the hippocampus and the PFC (Liu et al., 1997; Meaney et al., 1996, 1988). All of these changes induced by early maternal licking/grooming and related behavior involve alterations in the central circuitry of emotion that result in decreased responsivity to stress later in life.

The increased benzodiazepine receptor expression in the amygdala and LC likely play a role in the increased facility in inhibiting or regulating these systems following exposure to stress. Exposure to stress provokes an increase in the firing rate of neurons in the LC. Activity within the noradrenergic cell bodies in the LC is subject to inhibitory feedback regulation via α_2 adrenoreceptors. Thus, α_2 adrenoreceptor agonists decrease the firing rate of LC neurons and norepinephrine release at terminal sites. The increase in α_2 adrenoreceptor density and decrease in CRH receptor density in the LC (CRH infusion has been shown to alter the firing rate of LC neurons and to increase anxiety; see Weiss et al., 1994, for a review) are both likely to decrease fearfulness in the offspring of the high licking/grooming mothers. The increase in glucocorticoid receptors in both hippocampus and PFC is likely to play an important role in enhanced negative feedback efficacy of the adrenocortical axis. Among rats with less efficient negative feedback, elevated secretion of glucocorticoids was observed in response to stress, and later in life, basal elevations of this system occurred, leading to greater cumulative exposure to glucocorticoids. A variety of research indicates that exposure to elevated levels of glucocorticoids can accelerate hippocampal neuron loss and produce cognitive and affective impairments (McEwen, 1998).

There are several important implications of these animal data for understanding the role of plastic changes in the circuitry of emotion in humans. The findings briefly described above indicate the PFC, amygdala, and hippocampus are all sites where plasticity is known to occur. One of the interesting puzzles in the human literature on prefrontal asymmetries associated with affective style

is that although measures of baseline prefrontal asymmetries are stable in adults, they are not stable during early childhood (Davidson & Rickman, 1999). When we examined brain electrical measures of baseline prefrontal activation asymmetry over an 8-year period from 3 to 11 years of age in a cohort of approximately 65 children, we found little evidence of stability (Davidson & Rickman, 1999). This is a period during which pronounced plasticity is likely to occur in the central circuitry of emotion, particularly in the PFC, which is still undergoing important developmental change at least until puberty (Huttenlocher, 1990). An important challenge for future research will be to obtain better measures of life course events, parental influence and other important environmental factors and to relate the occurrences of these to shifts in patterns of prefrontal activation.

The animal data on the influence of environmental factors in the regulation of glucocorticoid receptor densities in the hippocampus provide some basis for understanding the possible effects of trauma on hippocampal structure and function. A number of studies have reported hippocampal atrophy on MRI in patients with posttraumatic stress disorder (Bremner et al., 1995, 1997; Stein, Koverola, Hanna, Torchia, & McClarty, 1997). In addition, recent studies have also found hippocampal atrophy in patients with major depression (Sheline, Sanghavi, Mintun, & Gado, 1999; Sheline, Wang, Gado, Csernansky, & Vannier, 1996) and alcoholism (Agartz, Momenan, Rawlings, Kerich, & Hommer, 1999). Of course, it is not possible from these studies to tease preexisting conditions apart from the influence of environmental stress or insult and conclusively establish causal influences. In addition, the functional significance of hippocampal volume reduction that is proportional to reductions in whole brain volume is not known at the present time (Agartz et al., 1999). Nevertheless, these points of convergence between the animal studies and human research are critical in developing a mechanistic understanding of how early stressful life events might influence the central circuitry of emotion, which in turn shapes patterns of emotional reactivity later in life.

Context and Regulation: Two Instances of Affective Plasticity

The role of context in the regulation of affective reactivity is relatively understudied, particularly at the human level. Numerous studies at the animal level have demonstrated the importance of context in the regulation of affective behavior and have highlighted the role of the hippocampus (Anagnostaras, Maren, & Fanselow, 1999) and interconnected structures (bed nucleus of the stria terminalis; Davis & Lee, 1998) in this type of process. Various forms of psychopathology that involve disorders of affect may be best conceptualized as disorders of the context-regulation of affect. For example, both mood and anxiety disorders typically involve the expression of normal emotion in inappropriate contexts. That is, the emotion expressed in these disorders would be normative and appropriate in certain contexts. Per the diagnostic criteria for major depression following bereavement, the depression must persist for more than 2 months to be labeled major depression (American Psychiatric Association, 1994). In other words, the continued expression of depressed affect beyond the context in which it is deemed appropriate is central to the diagnosis. In many of the anxiety disorders, the fear and other emotions

that might be experienced are perfectly normal emotions. They are simply expressed at inappropriate times in nonnormative contexts. Thus, the fear that a social phobic might experience in the course of interacting with a group of people is not in itself pathological. What makes the expression of the fear pathological is the fact that it is expressed in contexts in which most other individuals do not experience such fear.

In an effort to investigate context-inappropriate emotion in nonhuman primates, Kalin (Kalin & Shelton, 2000) examined 100 Rhesus monkeys with a series of behavioral tests called the Human Intruder Paradigm that has been used extensively in his laboratory (see Kalin & Shelton, 1989). These tests involve exposure of a monkey to three specific conditions. In one condition, the animal is alone (the alone condition); in a second condition, a human enters the room and exposes his profile to the animal (the no eye contact condition); in a third condition, the human enters the room and stares at the animal (the stare condition). Each of these conditions is presented for 10 min. During each condition, various behaviors of the animal are coded. In previous work, Kalin has demonstrated the differential sensitivity of the different behaviors to specific pharmacological manipulations (Kalin & Shelton, 1989). Normatively, monkeys freeze when exposed to the human profile. Interestingly, there are individual differences in freezing duration, and these differences are stable over time (Kalin, Shelton, Rickman, & Davidson, 1998). In response to both the alone and the stare conditions, the normative response of monkeys is to display little if any freezing, with other behaviors increasing in frequency during these conditions. When a very large group of animals was tested ($N = 100$), the pattern of normative behavior previously observed was confirmed at the group level (Kalin & Shelton, 2000). There is a highly significant difference in freezing duration among the conditions such that freezing is significantly higher during the no eye contact condition compared with the other two conditions. However, there are also marked individual differences, not only in the duration of freezing during the normative condition (no eye contact) but also in the duration of freezing during the other conditions. There were 3 animals in this group of 100 that displayed levels of freezing during the stare condition that were very high and indistinguishable from their freezing duration during the normative no eye contact condition (see Figure 3). Note that the freezing of this small subgroup of 3 was high during the no eye contact condition but that there were quite a few other animals who displayed levels of freezing that were comparable during this condition. However, all but these 3 animals turned off this response during the other conditions. These 3 animals can be said to have displayed context-inappropriate freezing. In analyses of biological data (prefrontal activation asymmetry and cortisol), it was found that these 3 animals had markedly more extreme patterns than their counterparts who froze for an identical duration of time during the normative context (Kalin & Shelton, 2000).

Although a mechanistic understanding of such context-inappropriate affective responding is not yet available, there are several issues that warrant comment. First, given the role of the hippocampus and bed nucleus of the stria terminalis that have been featured in rodent models of context conditioning (Fanselow, 2000; Davis & Lee, 1998), it is likely that these brain regions play a role in the context-regulation of affective responding in humans. It is noteworthy that in several disorders that are known to involve context-inappropriate affective responding, morphometric study of

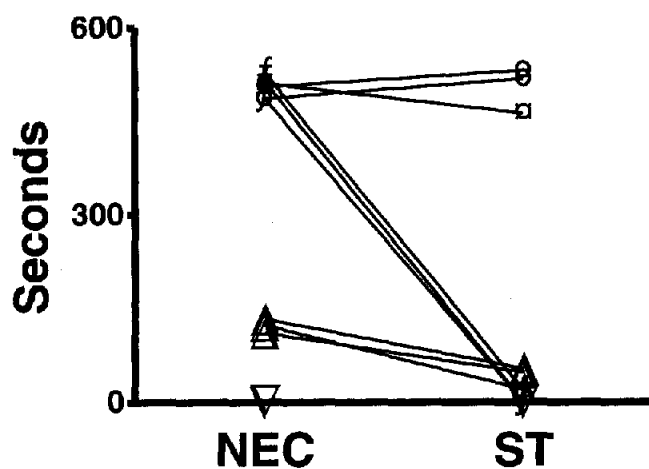


Figure 3. Freezing duration in seconds (out of a total of 600 s) in response to the no eye contact (NEC—exposure of the monkey to a profile of a human) and the stare (ST) conditions in four groups of animals: One group showed very long durations of freezing during the normative context (NEC) but then froze little during ST. Another group showed moderately elevated freezing during NEC and then showed little during ST. A third group showed virtually no freezing during either NEC or ST. Finally, the fourth group exhibited high levels of freezing in response to both NEC and ST. This is the group that displayed out-of-context freezing (i.e., during ST). The group of 3 animals who showed the out-of-context freezing were the only animals in a group of 100 to exhibit this pattern. From "The Regulation of Defensive Behaviors in Rhesus Monkeys: Implications for Understanding Anxiety Disorders," by N. H. Kalin and S. E. Shelton, in *Anxiety, Depression, and Emotion* (p. 63), edited by R. J. Davidson, 2000, New York: Oxford University Press. Copyright 2000 by the Oxford University Press. Reprinted with permission.

hippocampal volume with high resolution MRI has revealed significant atrophy (see, e.g., Bremner et al., 1995, 1997; Sheline et al., 1996, 1999). Such atrophy may arise as a consequence of exposure to elevated levels of cortisol, as several authors have hypothesized (Gold, Goodwin, & Chrousos, 1988; McEwen, 1998). At the human level, age-related declines in hippocampal volume have been related to elevated cortisol levels. The consequences of such age-related changes have been examined in the cognitive domain, specifically in measures of declarative memory that are thought to be hippocampally mediated (Lupien et al., 1998). However, there has been no study of which we are aware that has specifically related hippocampal morphometric differences to context-dependent affective responding. On the basis of the issues described above, we believe it is likely that glucocorticoid-induced changes in hippocampal structure will also be accompanied by profound affective changes and will impair an organism's ability to adaptively regulate emotion in a context-appropriate fashion. The affective consequences of hippocampal dysfunction may be as, if not more, important to the adaptive functioning of the organism as the cognitive changes that have been featured so prominently in the human literature. One of the important challenges in this area for the future will be to develop a better understanding of context from a human perspective given that most previous studies have been conducted at the animal level and have relied on simple manipulations of housing conditions to alter context.

The second issue that deserves emphasis here is the implications of the work on context and its role in shaping affective responding for assessing certain behavioral traits. We use behavioral inhibition as our example here, in part because the studies we have conducted in nonhuman primates have been designed to model human behavioral inhibition. In the developmental literature on human infants and toddlers, this temperamental characteristic has typically been assessed by observing behavioral signs of fearfulness and wariness in contexts of novelty and unfamiliarity (see, e.g., Kagan, Reznick, & Snidman, 1988). Thus, for example, behavioral inhibition (one measure of which is freezing) has been coded when toddlers are approached by unfamiliar strangers or bizarre-looking robots. These are situations where it is normative to show some wariness. In fact, the display of high levels of approach behavior in this context is the nonnormative, context-inappropriate response. As we noted above, there appear to be important differences between monkeys who express identically high levels of freezing during a normative context (exposure to the human profile) but differ in their duration of freezing during a nonnormative context (exposure to the human staring). Had the assessment period with these monkeys been restricted to the normative context, the two groups of high-freezing animals would have been classified identically. Only by including an assessment of their behavior in a nonnormative context were behavioral differences revealed, which helped to account for some of the variance in basal levels of prefrontal activation asymmetry and cortisol (Kalin & Shelton, 2000). These findings imply that our assessments of human behavioral inhibition may not be nearly as sensitive as they might. Rather than performing such assessments in the context-appropriate conditions of novelty and unfamiliarity, perhaps we should be measuring these temperamental characteristics in non-normative contexts. We hypothesize that individuals who habitually fail to regulate their affective responses in a context-sensitive fashion may have functional impairment of the hippocampus and/or stria terminalis. Such functional impairment may arise as a consequence of plastic changes in these regions as a function of cumulative exposure to elevated glucocorticoids (McEwen, 1998).

It has been known for some time that neurogenesis (the growth of new neurons), primarily in the dentate region of the hippocampus, can occur in the postnatal period in rodents (see Gould & McEwen, 1993, for a review). However, it has only recently been demonstrated that such plastic changes can occur in the adult human hippocampus as well (Eriksson et al., 1998). The fact that such neurogenesis can occur in adult humans raises the possibility that both salubrious as well as stressful conditions might influence this process and that these experience-induced hippocampal changes, in turn, can have significant affective and cognitive consequences. Kempermann, Kuhn, and Gage (1997) have demonstrated that exposure of adult mice to an enriched environment produced a 15% increase in granule cell neurons in the dentate gyrus of the hippocampus compared with littermates housed in standard cages. This basic phenomenon has been recently replicated in rats (Nilsson, Perfilieva, Johansson, Orwar, & Eriksson, 1999) and extended by demonstrating that the rats raised in an enriched environment who showed neurogenesis in the dentate gyrus also exhibited improved performance in a spatial learning test. Conversely, it has been shown that stress diminishes proliferation of granule cell precursors in the dentate region of adult

marmoset monkeys (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998).

Collectively, these findings highlight the plasticity of certain regions of the brain that persists into adulthood and raise the possibility that interventions, even those occurring during adulthood, not only can have effects on neuronal function but also can literally influence neurogenesis. The fact that the focus of this work is in the hippocampus indicates that a major substrate of context-dependent emotional responding is a key target for these experientially induced changes. It is likely that other brain regions as well exhibit plastic changes. Whether these involve neurogenesis or favor other mechanisms is a question that must be addressed in future work. For now, the extant findings provide a rationale for examining the impact of therapeutic interventions, both pharmacological and behavioral, as well as naturally occurring environmental stressors and stress buffers, on neuronal structure and the central circuitry of emotion that might underlie changes in affective style.

Finally, we turn our attention to another aspect of plasticity in affective responding—the group of phenomena we refer collectively to as affect regulation (see Gross, 1999, for a review). The importance of emotion regulation has been recognized by psychologists and philosophers for many years, although as a construct, emotion regulation remains vague. At the broadest level, it might be considered any process that maintains, accentuates, or attenuates emotional responses. Regulatory processes can be automatic or effortful, and they can be both statelike and traitlike. The clinical importance of emotion regulation can be seen by reviewing the diagnostic criteria for Axis I and II psychopathology in the *Diagnostic and Statistical Manual* (4th ed.; American Psychiatric Association, 1994), many of which include disturbances in regulatory processes. Because this literature has been recently reviewed by Gross (1999), only a few issues directly pertinent to our earlier discussion are addressed in this article. First, though this has not been emphasized in recent commentaries, it is difficult to rigorously separate the processes involved in the production of an emotion per se from those that might be involved in the regulation of that emotion. Given the fact of parallel processing in the brain, it is likely that these two components of emotional responding unfold as at least partially overlapping processes. Moreover, because different systems reflect different aspects of emotion and these occur at varying time courses, it is likely that regulatory processes may influence some systems more than others and also that such influences may exhibit temporal asynchrony. All of these facts collectively pose a formidable challenge to the investigator who wishes to obtain separate measures of emotion and regulation and to determine the influence of the latter on the former. Furthermore, there are likely to be important differences among individuals in different aspects of emotional regulation. In fact, such differences are likely to form key components of what we refer to as affective style.

In our earlier discussion of affective style, we introduced the idea of examining individual differences in the capacity to turn off negative emotions once they are turned on and the associated differences in the chronometry of negative affective responding. We (Jackson, Malmstadt, Larson, & Davidson, 2000) sought to develop a paradigm where we could crisply distinguish between emotion and regulation and to separate these processes in time. To do this, we chose to examine voluntary regulation⁵ of negative

emotion. In this experiment, participants were asked to suppress, maintain, or enhance their experiential responses to arousing negative pictures. Reasoning that successful emotion regulation should lead to more (in the enhance condition) or less (in the suppress condition) intense emotion, we used two well-validated measures of emotional state as dependent variables: startle eyeblink magnitude and corrugator region electromyogram activity (see Lang, 1995). To achieve the crucial experimental separation of initial emotion and subsequent regulation, we collected data in the presence of the emotional stimulus but prior to the regulation instruction, in addition to following the instruction. The instruction that was presented 4 s following the onset of a negative picture (total picture duration was 8 s) and simply instructed participants to either maintain, enhance, or suppress the emotion that they were experiencing. Replicating a vast literature, we indeed found that startle eyeblink magnitude and corrugator region activity were increased during the negative pictures, relative to neutral pictures prior to any presentation of an instruction to regulate. This enabled us to verify that the stimuli we used were indeed producing the intended emotion prior to the delivery of any instruction to regulate. We found that instructions to suppress a negative emotional response led to decreased eyeblink startle magnitude and corrugator activity, whereas instructions to enhance similar responses led to increases in both measures (compared within-subjects to the maintain condition).

In this study (Jackson et al., 2000), we also found that ability to suppress negative emotion was inversely correlated with ability to enhance negative emotion, suggesting that individual differences in the ability to regulate emotion as assessed in this paradigm vary with the valence and direction of the requested regulation instruction. Of great interest to us is whether the active effort to suppress negative emotion is associated with a phasic increase in the reciprocal coupling between the medial PFC and the amygdala resulting in prefrontal inhibition of amygdala activation as described above. This is a fully tractable problem and can be addressed by exploiting the time resolution that is now possible to achieve using event-related fMRI (Menon & Kim, 1999). Whether long-term traitlike and more automatic forms of emotion regulation are associated with actual structural changes in the brain is a question that has not yet been addressed in current research.

Summary, Future Trends, and Conclusions

This article was intended to showcase some modern developments in affective neuroscience and to illustrate how this approach might facilitate a more mechanistic understanding of the underlying subcomponents of emotion and affective style. Two major neural territories—the PFC and the amygdala—in the circuitry of emotion were featured. Both the dorsolateral and ventromedial sectors of the PFC have been associated with different aspects of emotion. Asymmetries in the PFC have been linked to approach and withdrawal systems, with sectors of the left PFC more associated with the approach system and certain forms of positive

⁵ Whether the mechanisms underlying voluntary emotion regulation are similar to or different from those that underlie automatic emotion regulation has not been rigorously addressed. Also unknown is whether individual differences in the voluntary regulation of emotion predict individual differences in more automatic forms of emotion regulation.

affect and other regions in the right PFC more associated with negative affect and withdrawal. Studies of patients with discrete PFC lesions, as well as studies using measures of regional brain activation in neurologically intact normal subjects and patients with psychiatric disorders, have provided evidence to support these proposals. The PFC is likely to play a role in affective working memory, a process critical to anticipating future affective outcomes (see, e.g., Watanabe, 1996). The amygdala is clearly important for several aspects of emotional processing, though there still remain many questions about its contributions to human emotion and affective style. It does appear to be the case that the amygdala is activated by stimuli that elicit certain forms of negative affect, particularly fear. It is also the case that individual differences in amygdala activation, both at baseline and in response to negative affect-arousing stimuli, account for significant variance in measures of emotion-related cognitive function (e.g., rapidity of aversive learning, recall of negative affective stimuli) and in self-report measures of negative dispositional mood. However, studies using discrete excitotoxic lesions of the amygdala in nonhuman primates that preserve fibers of passage suggest that the amygdala is not required for the expression of both behavioral and biological components of an anxious temperament. Other evidence suggests that the PFC may be a more critical site for the expression of these individual differences. The final two sections above addressed issues related to plasticity in the central circuitry of emotion and consequently, in affective style. Evidence at the animal level was reviewed to illustrate the profound impact of environmental events in shaping the neural circuitry of emotion. Data are now available that reveal changes down to the level of gene expression as a direct consequence of environmental manipulations. Moreover, in addition to the critical role of the early environment, new findings reveal neurogenesis in the human hippocampus in adults, indicating that plasticity continues unabated throughout the life course. The hippocampus and other interconnected structures were highlighted for their contribution to context-dependent affective responding. Stressors produce elevations in cortisol, which in turn result in hippocampal cell death and/or decreases in hippocampal neurogenesis. This chain of events provides one mechanism whereby negative life events can result in abnormalities in context-dependent emotional responses. We ended with a brief discussion of affect regulation. There are many forms of affect regulation involving both automatic and effortful/voluntary processing. It is likely that when traitlike regulatory strategies occur over a long duration of time, plastic changes in the central circuitry of emotion are produced.

One key issue for the future concerns the relation between affective style and health. We know that there are relations between individual differences in prefrontal activation asymmetry and immune function (Davidson et al., 1999; Kang et al., 1991), though whether these differences are related to health is not currently known. Autonomic changes have been described that accompany emotion regulation (see, e.g., Gross, 1998). Whether these autonomic changes, particularly when repeatedly invoked over time, have health consequences is also not known. A literature is beginning to develop on the key constituents of a salubrious lifestyle that may give rise to positive health (Ryff & Singer, 1998). Just what such positive events may do to shape the central circuitry of emotion requires future study.

Also critical to address in future research is the impact of interventions designed to promote positive affect on plastic

changes in the circuitry of emotion. Though there are some data on the impact of antidepressant medication on brain function (see, e.g., Bench, Frackowiak, & Dolan, 1995) and one study on the effects of cognitive therapy on regional glucose metabolism in patients with obsessive-compulsive disorder (Baxter et al., 1992), there are no data on plastic changes in the brain as a consequence of practicing methods designed to increase positive affect, such as meditation. The Dalai Lama himself has called attention to this possibility in his recent best seller *The Art of Happiness* (the Dalai Lama & Cutler, 1998). In this book, he discussed the implications of research on neural plasticity for increasing levels of happiness and explained:

The systematic training of the mind—the cultivation of happiness, the genuine inner transformation by deliberately selecting and focusing on positive mental states and challenging negative mental states—is possible because of the very structure and function of the brain. . . . But the wiring in our brains is not static, not irrevocably fixed. Our brains are also adaptable. (pp. 44–45)

Although the decade of the brain is just now ending, it is at the close of this decade that psychologists finally have both the theory and the methods to begin addressing some of the most important questions about human brain function that have for so long eluded rigorous study. Understanding how feeling is instantiated in the brain and using the brain's architecture to meaningfully parse the domain of emotion is now possible through the modern methods of affective neuroscience. Research on plasticity has revealed new information about and realistic hope for ways to shape the circuitry of emotion to promote increased well-being and positive affect. The downstream consequences of these patterns of neural activity for endocrine, autonomic and immune function can be studied to provide clues to the mechanistic understanding of how emotion might affect physical health and disease. Delineating the interaction between mind and body through the brain is now more tractable than ever before and it is our view that the domain of emotion—affective neuroscience—will be where new insights and improved understanding are most visible in this new century.

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