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Affective neuroscience and psychophysiology: Toward a synthesis

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Abstract

This article reviews the author's program of research on the neural substrates of emotion and affective style and their behavioral and peripheral biological correlates. Two core dimensions along which affect is organized are approach and withdrawal. Some of the key circuitry underlying approach and withdrawal components of emotion is reviewed with an emphasis on the role played by different sectors of the prefrontal cortex (PFC) and amygdala. Affective style refers to individual differences in valence-specific features of emotional reactivity and regulation. The different parameters of affective style can be objectively measured using specific laboratory probes. Relations between individual differences in prefrontal and amygdala function and specific components of affective style are illustrated. The final section of the article concludes with a brief discussion of plasticity in the central circuitry of emotion and the possibility that this circuitry can be shaped by training experiences that might potentially promote a more resilient, positive affective style. The implications of this body of work for a broader conception of psychophysiology and for training the next generation of psychophysiologists are considered in the conclusion.

Descriptors: Emotion, Affective style, Affective neuroscience, Prefrontal cortex, Amygdala

I was raised in this Society, having attended my first meeting as an eager graduate student in 1973 at the ripe young age of 22! I owe a tremendous debt of gratitude to the Society, to a number of its senior members and to my colleagues in the discipline who have nurtured my work and career and helped my research to flourish.

The scientific journey I will review in this article is about how the brain instantiates emotion and how best to parse the subcomponents of emotion by honoring the distinctions afforded by the neural circuitry involved. The phenomena of affective style will be featured, as one of the most salient characteristics of emotion is the fact that the same emotionally provocative event can elicit very different patterns of reactivity in different individuals. Also to be highlighted will be emerging work on the plasticity in the circuitry of emotion and what that can tell us about transforming emotional habits.

A major underlying theme of this work is that emotions serve complex functions that promote adaptation. Complex decisions—such as who to marry, which job to take—cannot be made solely on the basis of a cold calculus that involves the weighting of pros and cons in a formulaic prescription. Rather, such decisions are typically made by consulting our "feelings." Orchestrating the cascade of adjustments required to move closer toward our appetitive goals or to stop our ongoing stream of behavior in the face of a threat and increase our vigilance are equally complex and in the latter case, often have to be accomplished with great rapidity. These observations all point toward the fact that emotions are essential for successful adaptation, that they interact seamlessly with other cognitive processes, and that they support motivated behavior.

The first section of this article will present the approach and withdrawal as two of the core dimensions along which affective processes are organized. Some of the key circuitry that participates in aspects of the approach and withdrawal systems will then be described, with an emphasis on prefrontal cortex and the amygdala. The second section will then highlight the importance of affective style—individual differences in

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valence-specific features of emotional reactivity and responding and describe how different parameters of affective style can be measured objectively. Finally, the article will end with a short section on the role of plasticity in these systems.

The Anatomy of Approach and Withdrawal

Prefrontal Cortex

Although the prefrontal cortex (PFC) is often considered to be the province of higher cognitive control, it has also consistently been linked to various features of affective processing (see, e.g., Nauta, 1971, for an early preview). Miller and Cohen (2001) have recently outlined a comprehensive theory of prefrontal function based upon nonhuman primate anatomical and neurophysiological studies, human neuroimaging findings, and computational modeling. The core feature of their model holds that the PFC maintains the representation of goals and the means to achieve them. Particularly in situations that are ambiguous, the PFC sends bias signals to other areas of the brain to facilitate the expression of task-appropriate responses in the face of competition with potentially stronger alternatives. In the affective domain, we often confront situations where the arousal of emotion is inconsistent with other goals that have already been instantiated. For example, the availability of an immediate reward may provide a potent response alternative that may not be in the best service of the overall goals of the person. In such a case, the PFC is required to produce a bias signal to other brain regions that guide behavior toward the acquisition of a more adaptive goal, which in this case would entail delay of gratification. Affect-guided planning and anticipation that involves the experience of emotion associated with an anticipated outcome is the hallmark of adaptive, emotion-based decision making. Patients with lesions to certain zones of the PFC, particularly the ventromedial PFC, have been shown to exhibit profoundly impaired decision making (e.g., Damasio, 1994). Affect-guided anticipation is most often accomplished in situations that are heavily laden with competition from potentially stronger alternatives. In such cases in particular, we would expect PFC activation to occur. Certain disorders of emotional processing such as depression may be caused by abnormalities of affect-guided anticipation. For example, the failure to anticipate positive incentives and direct behavior toward the acquisition of appetitive goals are symptoms of depression that may arise from abnormalities in the circuitry that implements positive affect-guided anticipation. Our laboratory has contributed extensively to the literature on asymmetries in PFC function associated with approach- and withdrawal-related emotion and mood (e.g., Davidson & Irwin, 1999; Davidson, Marshall, Tomarken, & Henriques, 2000). In this context, we suggest that left-sided PFC regions are particularly involved in approach-related, appetitive goals. The instantiation of such goals, particularly in the face of strong alternative responses, requires left-sided PFC activation, and hypoactivation in these circuits has been linked to depression. Right-sided PFC regions, alternatively, are hypothesized to be particularly important in behavioral inhibition and vigilant attention that often accompanies certain aversive emotional states and traits. Whether right-sided PFC activation is a core feature underlying withdrawal behavior in general or behavioral inhibition and vigilant attention more specifically is a question to which we still do not have an adequate answer. The prototype of the behavioral inhibition process that we have hypothesized to be subserved by specific right PFC mechanisms has recently been captured in several neuroimaging studies that involve variants of a go/no go task where a dominant response set is established to respond quickly, except on those trials in which a cue to inhibit the response is presented. Two recent studies using event-related fMRI have found a lateralized focus of activation in the right lateral PFC (inferior frontal sulcus) to cues that signaled response inhibition that were presented in the context of other stimuli toward which a strong approach set was established (Garavan, Ross, & Stein, 1999; Konishi et al., 1999). This is the same region of right lateral PFC that has been found to be activated in a number of neuroimaging studies in which withdrawal-related negative affect has been elicited (for a review, see Davidson & Irwin, 1999).

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

Recent neuroimaging and electrophysiological studies suggest that the orbital and ventral frontal cortex in particular may be especially important for the representation of rewards and punishments, and different sectors within this cortex may emphasize reward versus punishment (Kawasaki et al., 2000; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). In particular, a left-sided medial region of the orbitalfrontal cortex (OFC) appears particularly responsive to rewards whereas a lateral right-sided region appears particularly responsive to punishments (O'Doherty et al., 2001). Kawasaki and colleagues recorded from single units in the right ventral PFC of patients with implanted depth electrodes for presurgical planning. They found these neurons in healthy tissue to exhibit short-latency responses to aversive visual stimuli. Such studies provide important clues regarding the circuitry that might be most relevant to understanding differences among individuals in affective style. For example, there are individual differences in responsivity to rewards versus punishments that can probed behaviorally using signal detection methods (Henriques & Davidson 2000; Henriques, Glowacki, & Davidson, 1994). Most normal individuals exhibit systematic modification of response bias to monetary reward, but some do not. Those who do not showed elevated depressed mood. We would also predict that left medial OFC would be hyporesponsive to manipulations of reward in such individuals whereas right lateral OFC response to punishment would either be normal or perhaps accentuated.

Amygdala

Although a link between amygdala activity and negative affect has been a prevalent view in the literature, particularly when examined in response to exteroceptive aversive stimuli (e.g., LeDoux, 2000), recent findings from invasive animal studies, human lesion, and functional neuroimaging studies are converging on a broader view that regards the amygdala's role in negative affect as a special case of its more general role in directing attention to affectively salient stimuli and issuing a call for further processing of stimuli that have major significance for

the individual. Extant evidence is consistent with the argument that the amygdala is critical for recruiting and coordinating cortical arousal and vigilant attention for optimizing sensory and perceptual processing of stimuli associated with underdetermined contingencies, such as novel, "surprising" or "ambiguous" stimuli (see also Davis & Whalen, 2001; Holland & Gallagher, 1999; Whalen, 1998). Most stimuli in this class may be conceptualized as having an aversive valence because we tend to have a negativity bias in the face of uncertainty (Taylor, 1991).

Both structural and functional differences in the amygdala have been reported in disorders of emotion, particularly depression. Structurally, several recent studies reported an association between enlargement of amygdala volume and depression. This association has been found in depressed patients with bipolar disorders (Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; Strakowski et al., 1999) as well as temporal lobe epilepsy (TLE; Tebartz van Elst, Woermann, Lemieux, & Trimble, 1999, 2000). In a recent study, Mervaala et al. (2000) observed significant asymmetry in amygdalar volumes (right smaller than left) in patients with major depressive disorder (MDD) but not the controls. In TLE patients with dysthymia, left amygdala volume was positively correlated with depression severity, as assessed with the BDI (Tebartz van Elst et al., 1999). Although these findings depict a relation between increased amygdalar volume and depression, it is important to stress that (a) the causal relations between the two entities are still unknown, and (b) some inconsistencies among studies are present. Indeed, some studies reported either decreased bilateral volume in the amygdala core nuclei (Sheline, Gado, & Price, 1998) or null findings (Ashtari et al., 1999; Coffey et al., 1993; Pantel et al., 1997). Although the reasons are still unclear, it is interesting to note that two null findings were found in geriatric depression (Ashtari et al., 1999; Pantel et al., 1997).

Functionally, abnormal elevations of resting rCBF or glucose metabolism in the amygdala have been reported in depression during both wakefulness (Drevets et al., 1992) and sleep (Ho et al., 1996; Nofzinger et al., 1999). In an FDG-PET study, Ho et al. reported increased absolute cerebral glucose metabolic in several brain regions, particularly the amygdala (+44%), in 10 unmedicated men with unipolar depression during a non-REM sleep period. Further, in his recent review, Drevets (2001) reports data from five consecutive studies, in which increased rCBF or glucose metabolism has been consistently replicated in depressives with familial MDD or melancholic features. In a postmortem study, 5-HT2 receptor density was significantly increased in the amygdala of depressive patients committing suicide (Hrdina, Demeter, Vu, Sotonyi, & Palkovits, 1993). Abnormally increased amygdalar activation has also been recently reported in bipolar depression (Ketter et al., 2001) and anxiety disorders, which often show a high degree of comorbidity with depression (Birbaumer et al., 1998; Liberzon et al., 1999; Rauch et al., 1996, 2000; Schneider et al., 1999; Semple et al., 2000; Shin et al., 1997). Further establishing a link between depression and amygdalar activation, two studies have reported a positive correlation between amygdalar activation and depression severity or dispositional negative affect in patients with MDD (Abercrombie et al., 1998; Drevets et al., 1992). After pharmacologically induced remission from depression, amygdalar activation has been observed to decrease to normative values (Drevets et al., 2001). In familial pure depressive disease, however, increased (left) amygdalar activation persists during the remitted phases (Drevets et al., 1992), suggesting, at least in some subtypes of depression, amygdalar dysfunction may be traitlike. Interestingly, remitted MDD patients showing symptom relapse as a consequence of serotonin depletion showed increased amygdalar activation prior to the depletion compared to those who will not relapse (Bremner et al., 1997). Finally, in one of the first fMRI studies using an activation paradigm, Yurgelun-Todd et al. (2000) reported higher left amygdalar activation for bipolar patients than controls in response to fearful faces.

In light of the pivotal role of the amygdala in recruiting and coordinating vigilant behavior toward stimuli with underdetermined contingencies, hyperactivation of the amygdala in major depression may bias initial evaluation of and response to incoming information. Although still speculative, this mechanism may rely on norepinephrine which (a) is often times abnormally elevated in depression (e.g., Veith et al., 1994), (b) is involved in amygdala-mediated emotional learning (Ferry, Roozendaal, & McGaugh, 1999), and (c) is affected by glucocorticoid secretion, which is often elevated in MDD (e.g., Carroll, Curtis, & Mendels, 1976). Thus, these findings may explain cognitive biases towards aversive or emotionally arousing information observed in depression.

Increased amygdalar activation in depression may also represent a possible biological substrate for anxiety, which is often comorbid with depression. In this respect, elevated levels of glucocortocoid hormones—which characterize at least some subgroups of patients with depression—may be especially relevant, because elevated glucocorticoid hormones have been shown to be associated with increased corticotropin-releasing hormone (CRH) in the amygdala. Increased CHR availability may increase anxiety, fear, and expectation for adversity (Schulkin, 1994).

In light of evidence suggesting a link between amygdalar activation, on one hand, and memory consolidation and acquisition of long-term declarative knowledge about emotionally salient information, on the other hand, the observations of dysfunctionally increased amygdalar activation in major depression are intriguing. As recently pointed out by Drevets et al. (2001), tonically increased amygdalar activation during depressive episodes may favor the emergence of rumination based on increased availability of emotionally negative memories. Although still untested, it is possible that these aberrant processes may rely on dysfunctional interactions between the amygdala, the PFC, and the anterior cingulate cortex (ACC). Notably, structural abnormalities have been reported in territories of the PFC intimately connected with the ACC (Drevets et al., 1997; Öngür, Drevets, & Price, 1998). ACC dysfunction, in particular, may lead to a decreased capability of monitoring potential conflict between memory-based ruminative processes and sensory information coming from the environment.

Affective Style

In several recent publications, we have suggested that the term *affective style* be used to denote a broad range of individual differences in different parameters of emotional reactivity. Davidson (1998a, 2000) has defined affective style as valence-specific features of emotional reactivity and affective responding. Specific parameters of affective style can be objectively measured including: (a) the threshold to respond, (b) the magnitude of the response, (c) the rise time to the peak of the response, (d) the

recovery function of the response, and (e) the duration of the response. The last three parameters all refer to different aspects of affective chronometry or the time course of emotional responding. We have proposed that time course variables are particularly germane to understanding individual differences that may reflect vulnerability to psychopathology, as certain forms of mood and anxiety disorders may be specifically associated with either a failure to turn off a response sufficiently quickly and/or an abnormally early onset of the response that may then result in a bypassing of normal regulatory constraints. The specific parameters of affective style described above all jointly govern in a complex fashion dispositional mood and other reportable characteristics that reflect affective style. In this section, research from my laboratory, which has examined relations between individual differences in both prefrontal and amygdala functions and their relation to measures that reflect affective style, will be summarized.

In both infants (Davidson & Fox, 1989) and adults (Davidson & Tomarken, 1989) there are large individual differences in baseline electrophysiological measures of prefrontal activation, and such individual variation is associated with differences in aspects of affective reactivity. In infants, Davidson and Fox reported that 10-month-old babies who cried in response to maternal separation were more likely to have less left- and greater right-sided prefrontal activation during a preceding resting baseline compared with those infants who did not cry in response to this challenge. In adults, we first noted that the phasic influence of positive and negative emotion elicitors (e.g., film clips) on measures of prefrontal activation asymmetry appeared to be superimposed upon more tonic individual differences in the direction and absolute magnitude of asymmetry (Davidson & Tomarken, 1989).

During our initial explorations of this phenomenon, we needed to determine if baseline electrophysiological measures of prefrontal asymmetry were reliable and stable over time and thus could be used as a traitlike measure. Tomarken, Davidson, Wheeler, and Kinney (1992) recorded baseline brain electrical activity from 90 normal subjects on two occasions separated by approximately 3 weeks. At each testing session, brain activity was recorded during eight 1-min trials, four eyes open and four eyes closed, presented in counterbalanced order. The data were visually scored to remove artifacts and then Fourier transformed. Our focus was on power in the alpha band (8–13 Hz), though we extracted power in all frequency bands (for methodological discussions, see Davidson, Chapman, Chapman, & Henriques, 1990; Davidson, Jackson, & Larson, 2000). We computed coefficient alpha as a measure of internal consistency reliability from the data for each session. The coefficient alphas were quite high, with all values exceeding .85, indicating that the electrophysiological measures of asymmetric activation indeed showed excellent internal consistency reliability. The test-retest reliability was adequate with intraclass correlations ranging from .65 to .75 depending upon the specific sites and methods of analysis. The major conclusion from this study was the demonstration that measures of activation asymmetry based upon power in the alpha band from prefrontal scalp electrodes showed both high internal consistency reliability and acceptable test-retest reliability to be considered a traitlike index. Similar findings have recently been obtained by Hagemann, Naumann, Thayer, and Bartussek (2002).

On the basis of our prior data and theory, we reasoned that extreme left and extreme right frontally activated subjects would show systematic differences in dispositional positive and negative affect. We administered the trait version of the Positive and Negative Affect Scales (PANAS; Watson, Clark, & Tellegen, 1988) to examine this question and found that the left-frontally activated subjects reported more positive and less negative affect than their right-frontally activated counterparts (Tomarken, Davidson, Wheeler, & Doss 1992; see Figure 1). More recently with Sutton (Sutton & Davidson, 1997) we showed that scores on a self-report measure designed to operationalize Gray's concepts of Behavioral Inhibition and Behavioral Activation (the BIS/BAS scales; Carver & White, 1994) were even more strongly predicted by electrophysiological measures of prefrontal asymmetry than were scores on the PANAS scales (see Figure 2). Subjects with greater left-sided prefrontal activation reported more relative BAS to BIS activity compared with subjects exhibiting more right-sided prefrontal activation. Independently, Harmon-Jones and Allen (1997) published findings that were consistent with Sutton and Davidson (1997), but see Hagemann, Naumann, Becker, Maier, and Bartussek (1998) and Davidson (1998b) for complications associated with attempts to replicate these basic findings.

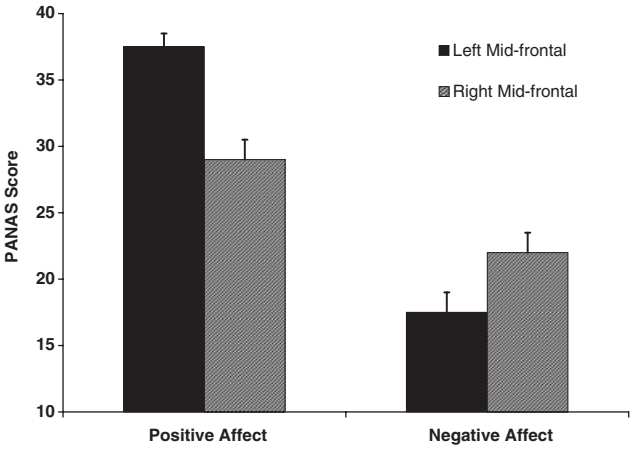

Figure 1. Dispositional positive and negative affect (from scores on the PANAS Scale) in subjects who were classified as extreme and stable left-frontally active ($N = 14$) and extreme and stable right-frontally active ($N = 13$) on the basis of electrophysiological measures of baseline activation asymmetries on two occasions separated by 3 weeks. (From Tomarken et al., 1992a.)

We also hypothesized that our measures of prefrontal asymmetry would predict reactivity to experimental elicitors of emotion. The model that we have developed over the past several years (for background, see Davidson, 1992, 1994, 1995, 1998a) features individual differences in prefrontal activation asymmetry as a reflection of a diathesis that modulates reactivity to emotionally significant events. According to this model, individuals who differ in prefrontal asymmetry should respond differently to an elicitor of positive or negative emotion, even when baseline mood is partialled out. We (Wheeler, Davidson, & Tomarken, 1993; see also Tomarken, Davidson, & Henriques, 1990) performed an experiment to examine this question. We presented short film clips designed to elicit positive or negative emotion. Brain electrical activity was recorded prior to the presentation of the film clips. Just after the clips were presented, subjects were asked to rate their emotional experience during the preceding film clip. In addition, subjects completed scales that were designed to reflect their mood at baseline. We found that

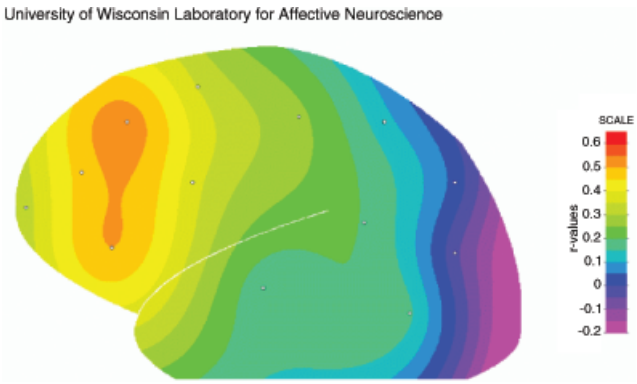

Figure 2. Relations between electrophysiological measures of asymmetry and the difference between the standardized score on the Behavioral Activation and Behavioral Inhibition Scales (BIS/BAS scales; Carver and White, 1994), $N = 46$. Electrophysiological data were recorded from each subject on two separate occasions separated by 6 weeks. The BIS/BAS scales were also administered on these two occasions. Data were averaged across the two time periods prior to performing correlations. The topographic map displays the correlations between alpha power asymmetry (log right minus log left alpha power; higher values denote greater relative left-sided activation) and the difference score between the standardized BAS minus BIS scales. After correlations were performed for each homologous region, a spline-interpolated map was created. The orange and red values of the scale denote positive correlations. The figure indicates that the correlation between the BAS-BIS difference score and the electrophysiology asymmetry score is highly positive in prefrontal scalp regions, denoting that subjects with greater relative left-sided activation report more relative behavioral activation compared with behavioral inhibition tendencies. The relation between asymmetric activation and the BAS-BIS difference is highly specific to the anterior scalp regions, as the correlation drops off rapidly more posteriorly. The correlation in the prefrontal region is significantly larger than the correlation in the parieto-occipital region. (From Sutton & Davidson, 1997.)

individual differences in prefrontal asymmetry predicted the emotional response to the films even after measures of baseline mood were statistically removed. Those individuals with more left-sided prefrontal activation at baseline reported more positive affect to the positive film clips and those with more right-sided prefrontal activation reported more negative affect to the negative film clips. These findings support the idea that individual differences in electrophysiological measures of prefrontal activation asymmetry mark some aspect of vulnerability to positive and negative emotion elicitors. The fact that such relations were obtained following the statistical removal of baseline mood indicates that any difference between left and right frontally activated subjects in baseline mood cannot account for the prediction of film-elicited emotion effects that were observed.

The relation between individual differences in brain electrical measures of prefrontal activation asymmetry and depression is a topic that has received extensive treatment in several recent articles. There has been a failure to replicate (Reid, Duke, & Allen, 1998) our initial findings of decreased left prefrontal activation in depression (Henriques & Davidson, 1990, 1991; Schaffer, Davidson, & Saron, 1983), though there have also been several published independent replications or conceptual replications (e.g., Allen, Iacona, Depue, & Arbisi, 1993; Field, Fox, Pickens, & Nawrocki, 1995). Moreover, using positron emission tomography, Baxter and colleagues (e.g., Baxter et al., 1989) have reported decreased activation in regions of left dorsolateral prefrontal cortex that were associated with depression severity (i.e., lower glucose metabolic rate predicted increased severity). Drevets et al. (1997) reported decreased activation in the subgenual prefrontal cortex in patients with depression that was more left-sided though the laterality of this finding is equivocal because of its proximity to the midline. Drevets et al. also reported a highly significant reduction in gray matter volume in the left subgenual PFC region. We have interpreted the decrease in left-sided prefrontal activation as a diathesis related to deficits in the approach system and in reward-related responding (Henriques & Davidson, 2000; Henriques et al., 1994). We also argued that this pattern of left prefrontal hypoactivation would only be found in certain subgroups of mood-disordered patients in light of the heterogeneity of the disorder (see Davidson, 1998b, for an extended discussion of both conceptual and methodological issues germane to this area). Most importantly, we have suggested that it is crucial to move beyond descriptive phenomenology and to examine with objective laboratory methods variations in reactivity to emotion elicitors in individuals with this hypothesized diathesis. We have proposed that individuals who display left prefrontal hypoactivation will show specific deficits in reactivity to reward, though the need to consider other components of the circuitry with which the prefrontal cortex is interconnected must be underscored in any effort to understand the neural bases of emotion and its disorders.

In addition to the studies described above using self-report and psychophysiological measures of emotion, we have also examined relations between individual differences in electrophysiological measures of prefrontal asymmetry and other biological indices that in turn have been related to differential reactivity to stressful events. Three recent examples from our laboratory include measures of immune function, cortisol, and corticotropin-releasing hormone. The latter two measures represent key molecules in the activation of a coordinated response to stressful events. Our strategy in each case was to examine relations between individual differences in measures of prefrontal activation asymmetry and these other biological indices. In two separate studies (Davidson, Coe, Dolski & Donzella, 1999; Kang et al., 1991), we examined relations between the prefrontal activation indices and natural killer (NK) activity, as declines in NK activity have been reported in response to stressful, negative events (Kiecolt-Glaser & Glaser, 1981). We predicted that subjects with greater right prefrontal activation would exhibit lower NK activity compared with their left-activated counterparts because the former type of subject has been found to report more dispositional negative affect, to show higher relative BIS activity, and to respond more intensely to negative emotional stimuli. In each of the two studies conducted with independent samples, we found that right-frontally activated subjects indeed had lower levels of NK activity compared to their left-frontally activated counterparts (Davidson et al., 1999; Kang et al., 1991). We also examined the magnitude of change in NK activity in response to stress and found that subjects with greater baseline levels of right prefrontal activation showed the largest magnitude decline in NK activity compared with other subjects (Davidson et al., 1999). Very recently, we (Rosenkranz et al., 2003) have extended this work to include measures of in vivo immune function. In a sample of 52 subjects between the ages of 57 and 60 years, we measured prefrontal activation asymmetry according to our usual methods. In addition, we administered an influenza vaccine and

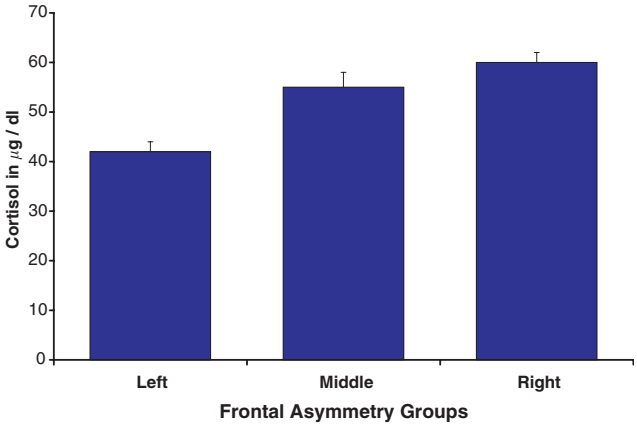

Figure 3. Basal morning plasma cortisol from 1-year-old rhesus monkeys classified as left ($N = 12$), middle ($N = 16$), or right ($N = 11$) frontally activated based upon electrophysiological measurements. (From Kalin et al., 1998.)

measured antibody titers in response to the vaccine at several internals following vaccination. We found that subjects with greater left-sided prefrontal activation at both baseline and in response to a negative affect challenge had greater antibody titers in response to influenza vaccine, suggesting more robust immunity in response to vaccination.

In collaboration with Kalin, our laboratory has been studying similar individual differences in scalp-recorded measures of prefrontal activation asymmetry in rhesus monkeys (Davidson, Kalin, & Shelton, 1992, 1993). Recently, we (Kalin, Larson, Shelton, & Davidson, 1998) acquired measures of brain electrical activity from a large sample of rhesus monkeys ($N = 50$). EEG measures were obtained during periods of manual restraint. A subsample of 15 of these monkeys was tested on two occasions 4 months apart. We found that the test-retest correlation for measures of prefrontal asymmetry was .62, suggesting similar stability of this metric in monkey and man. In the group of 50 animals, we also obtained measures of plasma cortisol during the early morning. We hypothesized that if individual differences in prefrontal asymmetry were associated with dispositional affective style, such differences should be correlated with cortisol, as individual differences in baseline cortisol have been related to various aspects of trait-related stressful behavior and psychopathology (see, e.g., Gold, Goodwin, & Chrousos, 1988). We found that animals with right-sided prefrontal activation had higher levels of baseline cortisol than their left-frontally activated counterparts (see Figure 3). As can be seen from the figure, it is the left-activated animals that are particularly low compared with both middle and right-activated subjects. Moreover, when blood samples were collected 2 years following our initial testing, animals classified as showing extreme right-sided prefrontal activation at age 1 year had significantly higher baseline cortisol levels when they were 3 years of age compared with animals who were classified at age 1 year as displaying extreme left-sided prefrontal activation. Similar findings were obtained with cerebrospinal fluid levels of CRH. Those animals with greater right-sided prefrontal activation showed higher levels of CRH (Kalin, Shelton, & Davidson, 2000; see Figure 4). These findings indicate that individual differences in prefrontal asymmetry are present in nonhuman primates, and that such differences predict biological measures that are related to affective style.

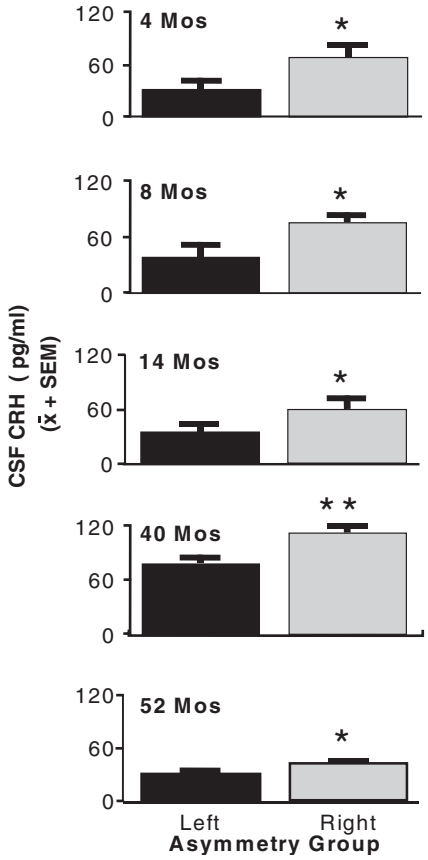

Figure 4. Differences between right- ($N = 9$) and left-prefrontally ($N = 10$) activated animals in cerebrospinal fluid measures of corticotropin releasing hormone at five different ages. The original classification of the animals as extreme right or left activated was performed on the basis of brain electrical activity data collected when the animals were 13 months of age. (From Kalin et al., 2000.)

With the advent of neuroimaging, it has become possible to investigate the relation between individual differences in aspects of amygdala function and measures of affective style. We have used PET with fluorodeoxyglucose (FDG) as a tracer to investigate relations between individual differences in glucose metabolism in the amygdala and dispositional negative affect. FDG-PET is well suited to capture traitlike effects because the period of active uptake of tracer in the brain is approximately 30 min. Thus, it is inherently more reliable than O15 blood flow measures because the FDG data reflect activity aggregated over a 30-min period. We have used resting FDG-PET to examine individual differences in glucose metabolic rate in the amygdala and its relation to dispositional negative affect in depressed subjects (Abercrombie et al., 1998). We acquired a resting FDG-PET scan as well as a structural MR scan for each subject. The structural MR scans are used for anatomical localization by coregistering the two image sets. Thus, for each subject, we used an automated algorithm to fit the MR scan to the PET image. Regions of interest (ROIs) were then drawn on each subject's MR scan to outline the amygdala in each hemisphere. These ROIs were drawn on coronal sections of subjects' MR images and the ROIs were then automatically transferred to the coregistered PET images. Glucose metabolism in the left and right amygdala ROIs were then extracted. The interrater reliability for the extracted glucose metabolic rate is highly

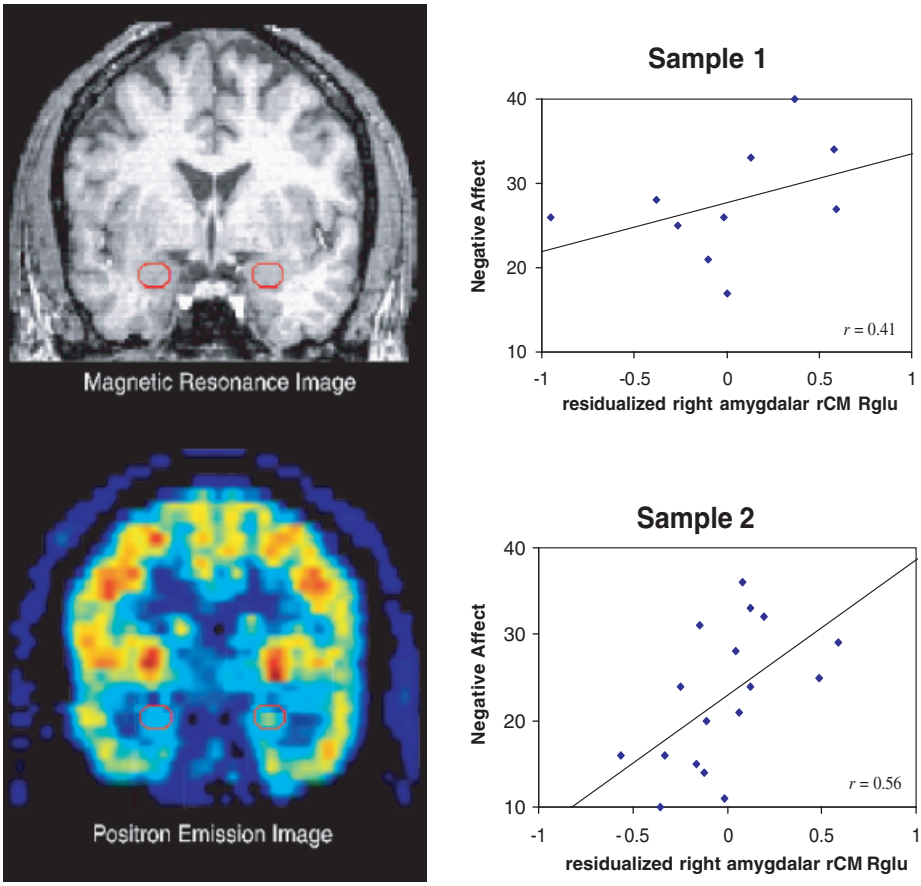

Figure 5. Images on the left indicate the MR on the top and corresponding PET image on the bottom from one subject to illustrate our method of MRI-coregistered regions-of-interest (ROIs) around the amygdala. ROIs were individually drawn for each subject around the amygdala, and glucose metabolism was then extracted from the PET image illustrated below. Scatter plots to the right display the relation between glucose metabolic rate (residualized for variations in whole brain metabolism) in the right amygdala and dispositional negative affect assessed with the PANAS for two independent samples of depressed patients tested on two different PET scanners. The scanner used for the data in the scatter plot on the bottom was one with the better spatial resolution (GE Advance). (From Abercrombie et al., 1998.)

significant, with intraclass correlations between two independent raters $\geqslant .97$. We found that subjects with greater glucose metabolism in the right amygdala report greater dispositional negative affect on the PANAS scale (see Figure 5). These findings indicate that individual differences in resting glucose metabolism in the amygdala are present and that they predict dispositional negative affect among depressed subjects.

In a small sample of 12 normal subjects, we (Irwin, Davidson, Kalin, Sorenson, & Turski, 1998) have been able to examine the relation between the magnitude of MR signal change in the amygdala in response to aversive compared with neutral pictures and dispositional negative affect on the PANAS scale. We correlated the average value of the pixels with the maximum Student's t from the left and right amygdala with dispositional negative affect. There was a robust correlation such that increased signal intensity in the right amygdala was associated with higher levels of negative affect (see Figure 6). A pixel in the fusiform gyrus that revealed robust activation by the aversive pictures was selected as a control region. We correlated the magnitude of activation in the pixel showing the maximal response in this region to the aversive pictures with dispositional negative affect and found no relation ($p > .5$). Moreover, the correlations in the amygdala and fusiform gyrus were found to be significantly different. The findings from the fMRI and PET

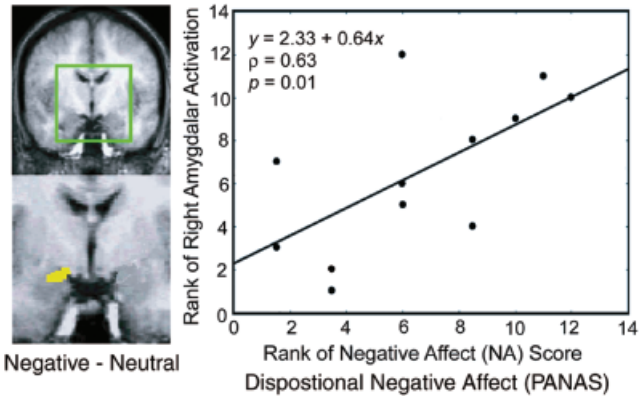

Figure 6. Coronal image in the top left indicates the region that contains the amygdala and that is zoomed in upon in the bottom left image. The bottom left image also contains data showing activation of the right amygdala (right side of the brain is on the left side of the image) in response to unpleasant versus neutral pictures from the International Affective Picture Series (Lang et al., 1995; from Irwin et al., 1998). The scatter plot at the right indicates the relation between the magnitude of MR signal change in the right amygdala and the rank ordering of dispositional negative affect as measured by the PANAS. (From Irwin et al., 1998.)

studies of amygdala function indicate that individual differences in both tonic activation and phasic activation in response to aversive stimuli predict the intensity of dispositional negative affect.

Emotion Regulation: A Key Component of Affective Style

One of the key components of affective style is the capacity to regulate negative emotion and specifically to decrease the duration of negative affect once it arises. We have suggested in several recent articles that the connections between the PFC and amygdala play an important role in this regulatory process (Davidson, 1998a, 2000; Davidson & Irwin, 1999; Davidson, Putnam & Larson, 2000). In two recent studies, we (Jackson, Malmstadt, Larson, & Davidson, 2000; Larson et al., 1998) examined relations between individual differences in prefrontal activation asymmetry and the emotion-modulated startle. In these studies, we presented pictures from the *International Affective Picture System* (Lang, Bradley & Cuthbert, 1995) while acoustic startle probes were presented and the EMG-measured blink response from the orbicularis oculi muscle region was recorded (see Sutton, Davidson, Donzella, Irwin, & Dottl, 1997, for basic methods). Startle probes were presented both during the slide exposure and at various latencies following the *offset* of the pictures, on separate trials. We interpreted startle magnitude during picture exposure as providing an index related to the generation of the emotional response, whereas startle magnitude following the offset of the pictures was taken to reflect the recovery from emotional challenge. Used in this way, startle probe methods can potentially provide new information on the time course of emotional responding. We expected that individual differences during actual picture presentation would be less pronounced than individual differences following picture presentation because an acute emotional stimulus is likely to pull for a normative response across subjects, whereas individuals are more likely to differ once the stimulus has terminated. Similarly, we predicted that individual differences in prefrontal asymmetry would account for more variance in predicting magnitude of recovery (i.e., startle magnitude poststimulus) than in predicting startle magnitude during the stimulus. Our findings in both studies were consistent with our predictions and indicated that subjects with greater right-sided prefrontal activation show a larger blink magnitude following the offset of the negative stimuli, after the variance in blink magnitude *during* the negative stimulus was partialled out. Measures of prefrontal asymmetry did not reliably predict startle magnitude during picture presentation. The findings from this study are consistent with our hypothesis and indicate that individual differences in prefrontal asymmetry are associated with the time course of affective responding, particularly the recovery following emotional challenge. In a related study, we have found that subjects with greater baseline levels of left prefrontal activation are better able to voluntarily suppress negative affect (see Jackson, Burghy, Hanna, Larson & Davidson, 2000; Jackson, Malmstadt et al., 2000). Moreover, in an initial study using functional MRI we have demonstrated that when subjects are instructed to voluntarily regulate their negative emotion, reliable changes in amygdala signal MR signal intensity are found (Schaefer et al., 2002).

The findings from these studies indicate that individual differences in prefrontal activation may play an important role in emotion regulation. Individuals who report greater dispositional negative affect and who show increased reactivity to stressful events are more likely to be those individuals who have difficulty regulating negative affect and specifically in modulating the intensity of negative affect once it has been activated.

Plasticity in the Central Circuitry of Emotion

The circuitry that underlies emotion regulation, in particular, the amygdala and prefrontal cortex, have both been targets of intensive study of plasticity (see Davidson, Jackson, & Kalin, 2000, for extensive discussion). In a series of elegant studies in rodents, Meaney and his colleagues (Francis & Meaney, 1999) have demonstrated that an early environmental manipulation in rats—frequency of maternal licking/grooming and arched-back nursing—produces a cascade of biological changes in the offspring that shape the central circuitry of emotion and, consequently, alter the animal's behavioral and biological responsivity to stress. For example, the offspring of mothers high in licking and grooming show increased central benzodiazepine receptor densities in various subnuclei of the amygdala as well as in the locus coeruleus (LC), increased α_2 adrenoreceptor density in the LC, and decreased CRH receptor density in the LC (Caldji et al., 1998). In other research, Meaney and coworkers have reported that that rats exposed to high licking/grooming mothers exhibited a permanent increase in concentrations of receptors for glucocorticoids in both the hippocampus and the prefrontal cortex (Liu et al., 1997; Meaney, Aitken, van Berkel, Bhatnagar, & Sapolsky, 1988; Meaney et al., 1996). All of these changes induced by early maternal licking/grooming and related behavior involve alterations in circuitry crucial to emotion and emotion regulation. The result of these early environmental influences is to decrease behavioral and biological responsivity to stress later in life. In more recent work, Gage and his collaborators (Kemperman, Gast, & Gage, 2002) have found that enriched environmental experience results in large-scale increases in neurogenesis in the hippocampus in adult animals, suggesting that these environmental effects are not restricted to early life events.

These findings in animals raise the possibility that similar effects may transpire in humans. There are clearly short-term changes in brain activation that are observed during voluntary emotion regulation, as noted above. Whether repeated practice in techniques of emotion regulation lead to more enduring changes in patterns of brain activation is a question that has not yet been answered in extant research. There are limited data available that indicate that cognitive behavioral therapy for certain disorders (e.g., obsessive compulsive disorder) produce changes in regional brain activity that are comparable to those produced by medication (Baxter et al., 1992; Furmark et al., 2002). What is absent are data on plastic changes in the brain that might be produced by the practice of methods specifically designed to increase positive affect, such as meditation. In a recent study, we (Davidson et al., in press) examined changes in anterior activation asymmetry produced by an 8-week course in mindfulness meditation-based stress reduction (Kabat-Zinn et al., 1992). We compared subjects randomly assigned to a mediation group or a wait-list control group on measures of baseline brain electrical asymmetry (in addition to other measures) before and after the 8-week intervention. The intervention consisted of one 2.5-hr class per week, along with a request that subjects practice 45 min per day. We found that subjects in the meditation group showed an increase in left-sided anterior activation whereas subjects in the wait-list control group showed a change in the opposite direction. We also administered an influenza vaccine following the completion of the 8-week

course to subjects in both the meditation and control groups. Remarkably, we found that subjects in the meditation group showed a larger increase in antibody titers to the influenza vaccine compared with the controls, and that the magnitude of shift toward more left-sided anterior activation was associated with a larger increase in antibody titers.

Summary and Conclusions

Psychophysiology has historically been at the center of research efforts dedicated to furthering our understanding of how mental events are instantiated in our biology. In our efforts to become methodologically sophisticated, some of the conceptual strengths of our approach have receded into the background. Moreover, our discipline has tended to become overly identified with the specific methods that are most commonly deployed to assess biological function with surface electrodes. I hope that the program of research featured in this article and in my career will stand as a plea for a more open and inclusive psychophysiology and will also serve as a catalyst for training the next generation of psychophysiologists in a broader and more interdisciplinary fashion. Unlike our neighboring discipline of brain imaging, psychophysiology has always included both central and peripheral systems in its purview and has been dedicated to understanding interaction between central and peripheral biological systems since its inception. This is clearly a strength on which we should continue to capitalize and it bodes well for the continued relevance and future success of our discipline.

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