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Asymmetric brain function, affective style, and psychopathology: The role of early experience and plasticity

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Abstract

A model of asymmetric contributions to the control of different subcomponents of approach- and withdrawal-related emotion and psychopathology is presented. Two major forms of positive affect are distinguished. An approach-related form arises prior to goal attainment, and another form follows goal attainment. The former is hypothesized to be associated with activation of the left prefrontal cortex. Individual differences in patterns of prefrontal activation are stable over time. Hypoactivation in this region is proposed to result in approach-related deficits and increase an individual's vulnerability to depression. Data in support of these proposals are presented. The issue of plasticity is then considered from several perspectives. Contextual factors are superimposed upon tonic individual differences and modulate the magnitude of asymmetry. Pharmacological challenges also alter patterns of frontal asymmetry. A diverse array of evidence was then reviewed that lends support to the notion that these patterns of asymmetry may be importantly influenced by early environmental factors that result in enduring changes in brain function and structure.

For more than 100 years, scientists and clinicians have suspected that the two cerebral hemispheres were differentially specialized for different types of affective processes (e.g., Jackson, 1878). The earliest clues about possible differential function of the two cerebral hemispheres in the affective domain came from observations of patients with unilateral brain lesions. Patients with left hemisphere damage were often described as depressed, while patients with right hemisphere damage were frequently indifferent to their neurological insult and occasionally euphoric. While unsystematic and sporadic, these early clinical observations provided the catalyst for a modern reexamination of the role of the two cerebral hemispheres in emotion.

Beginning about 25 years ago, Gainotti (1972) began to study the emotional behavior of patients with unilateral left and right hemisphere lesions. Though there is still some controversy about just what these findings actually demonstrate (see Davidson, 1993; Gainotti, Caltagirone, & Zoccolotti, 1993), the studies did show that certain symptoms associated with negative affect (e.g., crying) were more prevalent following left hemisphere damage, while other behaviors that typically are associated

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with positive affect (e.g., joking) are more often associated with right hemisphere damage.

There were several critical methodological shortcomings of these early studies. Three stand out as most significant. First is the failure to separate patients by caudality of lesion. Based on recent findings (to be discussed later), it is essential that lesion location along the rostral-caudal plane be carefully specified. Cerebral asymmetry is not homogeneous; there are important functional differences between anterior and posterior cortical zones that must be taken into account in any comprehensive account of emotion.

The second methodological shortcoming of the early work is the causal assumption entailed in the expectation that a lesion in a particular site will produce a specific form of affective change. Studies were performed that examined the dispositional mood state of patients with unilateral lesions. There was the expectation that the occurrence of the lesion would lead necessarily to the affective change in question. Implicit was the assumption that changes in activation asymmetry produced by a unilateral lesion were sufficient for the production of an affective change. This view has been challenged on both theoretical and empirical grounds (see Davidson, 1993). It is clear from the work on patients with brain lesions that patients with left prefrontal lesions are not necessarily depressed (e.g., House, Dennis, Warlow, Hawton, & Molyneux, 1990). Electrophysiological studies demonstrate that neurologically intact subjects with hypoactivation in the left frontal region are not necessarily depressed (see Davidson, 1993, for a review). These findings call into question the assumption that anterior activation asymmetries are sufficient for the production of particular emotional states. I have proposed elsewhere that anterior activation asymmetry may serve as a diathesis that increases an individual's *vulnerability* to particular types of emotions and psychopathology, given the requisite elicitors. Thus, while an individual with decreased left prefrontal activation would not be expected to be depressed, they would be expected to show increased levels of sadness and decreased levels of approach and decreased reactivity to reward in response to specific challenges. Data that support this proposition will be presented later.

The third methodological shortcoming is related to the second and concerns the crude measures of affect utilized in most previous studies of brain-lesioned patients. The typical study of this kind used self-report or observer ratings to make inferences about the patient's affective state. While these procedures may be satisfactory for making categorical diagnoses, they are insufficient to reveal subtle affective changes. Moreover, in light of the fact that patients with unilateral lesions may not necessarily display a dispositional affective change, investigations that move beyond simple phenomenology are required. What is needed are studies that use specific probes of emotion, with sensitive and objective indicators to verify their presence.

The Anatomy of Approach and Withdrawal

Although the focus of my empirical research has been on measures of frontal brain activity, it must be emphasized at the outset that the circuit instantiating emotion in the human brain is complex and involves a number of interrelated structures. Preciously few empirical studies using modern neuroimaging procedures that afford a high degree of spatial resolution have yet been performed. Therefore, hypotheses about the set of structures that participate in the production of emotion must necessarily be speculative and based, to a large extent, on the information available from the animal literature (e.g., LeDoux, 1987) and from theoretical accounts of the processes involved in human emotion.

Based on the available strands of theory and evidence, I have proposed two basic circuits each mediating different forms of motivation and emotion. The approach system

facilitates appetitive behavior and generates certain types of positive affect that are approach-related (e.g., enthusiasm, pride). This form of positive affect is usually generated in the context of moving toward a desired goal (see Lazarus, 1991, and Stein & Trabasso, 1992, for theoretical accounts of emotion that place a premium on goal states). The representation of a goal state in working memory is hypothesized to be implemented in dorsolateral prefrontal cortex, particularly on the left side. The basal ganglia are hypothesized to be involved in the expression of the abstract goal in action plans. The amygdala is hypothesized to be involved in the feeling state with projections from it to the hypothalamus providing the autonomic supports for the action. In addition, the learning of associations between particular sensory stimuli and their reward-related properties is likely to depend on the amygdala. Other structures are also likely to be implicated. Depending on the modality of the emotion-eliciting stimulus, different regions of sensory and association cortex will be required. Those portions of parietal and prefrontal cortex as well as the cingulate that have been implicated in various forms of attention might also be activated during approach-related emotions since we are likely to focus attention on those portions of the stimulus field that are most important for goal acquisition.

It should be noted that the activation of this approach system is hypothesized to be associated with one particular form of positive affect and not all forms of such emotion. It is specifically predicted to be associated with *pre-goal attainment positive affect*, that form of positive affect that precedes the acquisition of an appetitive goal. *Post-goal attainment positive affect* represents another form of positive emotion that is not expected to be associated with activation of dorsolateral prefrontal cortex. This latter type of positive affect may be phenomenologically experienced as contentment and is expected to occur when the prefrontal cortex goes off-line after a desired goal has been achieved.

Lawful individual differences can enter into many different stages of the approach system. Such individual differences and their role in modulating vulnerability to psychopathology will be considered in detail later. For the moment, it is important to underscore two issues. One is that there are individual differences in the tonic level of activation of the approach system that alters an individual's propensity to experience approach-related positive affect. Second, there are likely to be individual differences in the capacity to shift between pre- and post-goal attainment positive affect and in the ratio between these two forms of positive affect. Upon reaching a desired goal, some individuals will immediately replace the just-achieved goal with a new desired goal and so will have little opportunity to experience post-goal attainment positive affect or contentment. There may be an optimal balance between these two forms of positive affect, although this issue has never been studied.

There appears to be a second system concerned with the neural implementation of withdrawal. This system facilitates the withdrawal of an individual from sources of aversive stimulation and generates certain forms of negative affect that are withdrawal related. Both fear and disgust are associated with increasing the distance between the organism and a source of aversive stimulation. From invasive animal studies and human neuroimaging studies, it appears that the amygdala is critically involved in this system (e.g., LeDoux, 1987). In addition, the temporal polar region also appears to be activated during withdrawal-related emotion (e.g., Reiman, Fusselman, Fox, & Raichle, 1989; but see Drevets, Videen, MacLeod, Haller, & Raichle, 1992). These effects, at least in humans, appear to be more pronounced on the right side of the brain (see Davidson, 1992, 1993, for reviews). In the human electrophysiological studies, the right frontal region is also activated during withdrawal-related negative affective states (e.g., Davidson, Ekman, Saron, Senulis, & Friesen, 1990). At pres-

ent, it is not entirely clear whether this electroencephalographic (EEG) change reflects activation at a frontal site or the activity recorded at the frontal scalp region is volume conducted from other cortical loci. The resolution of this uncertainty must await additional studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), which have sufficient spatial resolution to differentiate among different anterior cortical regions. In addition to the temporal polar region, the amygdala, and possibly the prefrontal cortex, it is also likely that the basal ganglia and hypothalamus are involved in the motor and autonomic components, respectively, of withdrawal-related negative affect (see Smith, DeVito, & Astley, 1990).

The nature of the relation between these two hypothesized affect systems also remains to be delineated. The emotion literature is replete with different proposals regarding the interrelations among different forms of positive and negative affect. Some theorists have proposed a single bivalent dimension that ranges from unpleasant to pleasant affect, with a second dimension that reflects arousal (e.g., Russell, 1980). Other theorists have suggested that affect space is best described by two orthogonal positive and negative dimensions (e.g., Watson & Tellegen, 1985). Still other workers have suggested that the degree of orthogonality between positive and negative affect depends on the temporal frame of analysis (Diener & Emmons, 1984). This formulation holds that, when assessed in the moment, positive and negative affect are reciprocally related, but when examined over a longer time frame (e.g., dispositional affect) they are orthogonal. It must be emphasized that these analyses of the relation between positive and negative affect are all based exclusively on measures of self-report; therefore, their generalizability to other measures of affect are uncertain. However, based on new data, to be described later, we believe that a growing corpus of data does indeed indicate that one function of positive affect is to inhibit concurrent negative affect.

Individual Differences in Anterior Brain Function and Their Relation to Emotional Reactivity and Vulnerability to Psychopathology

Most of our work to date on this topic has emphasized asymmetric patterns of activation recorded from prefrontal and anterior temporal scalp sites using quantitative electrophysiological measures. There are a number of advantages and disadvantages of using such electrophysiological measures to make inferences about patterns of asymmetric activation. The chief advantage is that the procedures are totally noninvasive. This allows these measures to be used with infants and children and to be repeated on the same subjects. Other neuroimaging procedures are more invasive and require more cooperation on the part of the subjects, resulting in them being less well suited for studies with children. Another advantage of electrophysiological procedures is that they are relatively inexpensive. When coupled with their noninvasive nature, these virtues enable an investigator to test large numbers of subjects, which is often necessary for certain types of studies where the focus is on individual differences. The chief disadvantage is the relatively poor spatial resolution afforded by these techniques. They are useful for broad regional localization but lack the precision necessary for more fine-grained functional anatomic studies.

It should also be emphasized that scalp electrophysiological measures as used in our laboratory primarily reflect cortical activity and, thus, will be sensitive to only some of the structures implicated in the approach and withdrawal circuits already described. Based on our extant empirical data, it appears as if important individual differences are present in these cortical circuits. However, much more research using other methods is required to determine whether or not similar patterns are present in subcortical structures. In our current ongoing research, we are using both brain electrical activity measures and measures of regional glucose metabolism assessed with PET. The PET methods enable us to examine the detailed

cortical and subcortical circuitry that might contribute to the electrophysiological asymmetries we observe from scalp measures.

Over the past 5 years, we have conducted an extensive program of research on relations between individual differences in patterns of anterior asymmetry in measures of brain electrical activity and their relation to dimensions of emotion and vulnerability to psychopathology. I will briefly review salient highlights of this work to provide the background for a consideration of the causes of these asymmetries and plasticity in the shaping of these patterns of brain function.

Before describing the results of our studies, it would be informative for readers to have a clear understanding of our electrophysiological procedures and how they are applied in the study of individual differences. By placing surface electrodes on homologous scalp locations, electrical activity from each side of the brain can be measured. A wealth of data indicates that a decrease in synchronous activity in the alpha band (8–13 cycles/s) in adults is associated with activation. The peak frequency of waking synchronous activity in infants and toddlers is lower than in the adult but functionally is the same as in adults (see Segalowitz & Berge, in press, for a review). Alpha activity has been likened to a cortical idling rhythm. When populations of cortical neurons become activated, there is a decrease in amplitude and, sometimes, an increase in frequency of the signal. This suppression of alpha power in adults has been used as a measure of activation (Pivik et al., 1993; Shagass, 1972). Alpha power is extracted from the background EEG by subjecting the signal to Fourier analysis, which decomposes the complex waveform into underlying frequency components. Power (squared voltage) in any frequency band can then be quantified. When an individual performs a task that has been well validated as a measure of left or right hemispheric function, there is corresponding change in the asymmetry of alpha power recorded from homologous electrode sites (Davidson, Chapman, Chapman, & Henriques, 1990). Other recent evidence indicates that the magnitude and duration of alpha suppression recorded with both brain electrical and magnetic techniques from areas over visual cortex is strongly associated with measures of performance in a mental rotation task (Michel, Kaufman, & Williamson, 1994).

In addition to phasic changes in synchronous activity that are induced by specific tasks, there are also individual differences in the magnitude and direction of these brain electrical asymmetries. Such asymmetries can be recorded during baseline periods when no specific task is provided to the subject. It appears that phasic changes in brain electrical asymmetry are superimposed on more tonic individual differences in these measures (see Davidson & Tomarken, 1989, for review). There has been some question in the literature regarding the reliability and stability of such resting measures of asymmetry. In most studies where such resting measures are obtained, particularly in adults, subjects are not provided with any explicit task. They are simply instructed to sit quietly and rest, sometimes with eyes open and at other times with eyes closed. In studies with toddlers, they are sometimes provided with a very simple task that putatively does not induce any asymmetric effects, such as watching a video of foveally presented simple shapes. These simple tasks are designed to help the children fixate their eyes to minimize artifact. In studies we are currently conducting with subjects between 2 and 4 years of age, the children watch a video monitor that displays a circle that progressively shrinks in diameter. They are told to keep still when the circle is visible and that when the circle disappears, they are free to move. The trial (usually 30 s in length for children) is over (i.e., data collection stops) when the circle disappears. We have found that such simple tasks do not change the direction and magnitude of brain electrical asymmetry compared with a pure resting condition and have the advantage of motivating the children to remain relatively still so that the quality of the data is improved. The key issue for the study of

individual differences in such patterns of asymmetry is whether the data recorded during such resting or near-resting conditions are reliable.

Recently, we (Tomarken, Davidson, Wheeler, & Kinney, 1992) performed a study with a relatively large sample size (N = 90) for a psychophysiological study. Young adult subjects were tested on two occasions separated by approximately 3 weeks under pure resting conditions. During each session, brain electrical activity was measured during 8 1-min trials, half conducted with eyes open and half with eyes closed, presented in counterbalanced order. The questions we posed were simple ones that are the same type of question asked about any measure that putatively reflects a trait-like attribute: Is there stability of measures of anterior asymmetry across the 3-week period? Do the measures of anterior asymmetry show adequate internal consistency reliability across the eight separate trials within a session? The data from this study provided firm conclusions for each question. Our analyses focused on asymmetry from two anterior regions that have been implicated as important in affective processing—the midfrontal region (recorded from the F3 and F4 electrode sites) and the anterior temporal region (recorded from the T3 and T4 electrode sites). We found that the asymmetry score from each session (computed as the difference in the log-transformed alpha power from homologous sites, aggregated across the 8 1-min trials) was moderately stable across the 3-week period, with test-retest intraclass correlations ranging from .65 to .73, depending on site and reference electrode. The internal consistency reliability was assessed by computing coefficient alpha across the eight 1-min trials within each session. The internal consistency reliability for these measures was high, with values exceeding .85. The findings from this study indicate that resting baseline measures of anterior asymmetry show the psychometric qualities that are required of an index that is used to assess a trait-like attribute—adequate test-retest stability and internal consistency reliability.

In a series of studies, we have used such baseline measures of asymmetric activation and examined relations between individual differences in such measures and other behavioral and biological indicators of affective reactivity and vulnerability to psychopathology.

In young adults, we first demonstrated that subjects selected on the basis of stable and extreme scores on our measure of prefrontal asymmetry from a sample of 90 subjects reported different patterns of positive and negative dispositional mood (Tomarken, Davidson, Wheeler, & Doss, 1992). As Figure 1 shows, subjects with left-sided frontal activation report more positive and less negative affect on Watson et al.'s (Watson, Clark, & Tellegen, 1988) Positive and Negative Affect Scale (PANAS) measure. The PANAS positive scale taps a form of approach-related positive affect. Consider some of the items that subjects would rate as self-descriptive who score high on the positive scale: enthusiastic, proud, excited. These data indicate that subjects with greater relative left-sided frontal activation are more likely to endorse such items compared with subjects selected on the basis of the opposite asymmetry pattern. In this same study, we also examined the PANAS scores of subjects selected to be stable and extreme in anterior temporal asymmetry and found that their pattern of data resembled the findings from the frontal extreme groups. The Affect Intensity Measure (AIM; Larsen & Diener, 1987) was used to assess overall differences in affective reactivity among subjects with different patterns of anterior asymmetry. There was no relation between scores on the AIM and either frontal or anterior asymmetry, suggesting that the relations we observed with the PANAS were valence specific and were not simply a function of differences among subjects in overall emotional reactivity.

It is important to emphasize that the data from the study just described were based on the dispositional form of the PANAS scale. In this form, subjects are asked to rate how they feel *in general*. In a series of other studies, we have examined the relation between

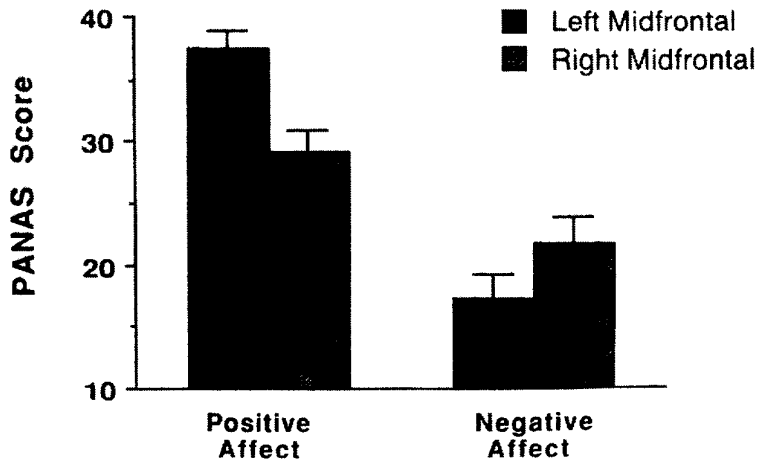

Figure 1. Scores on Watson et al.'s (1988) Positive and Negative Affect Scale (PANAS) administered in trait form, separately for subjects selected on the basis of extreme and consistent left and right frontal activation. From "Individual Differences in Anterior Brain Asymmetry and Fundamental Dimensions of Emotion" by A. J. Tomarken, R. J. Davidson, R. E. Wheeler, and R. C. Doss, 1992, *Journal of Personality and Social Psychology, 62*, p. 681. Copyright 1992 by the American Psychological Association. Reprinted by permission.

individual differences in anterior asymmetry and reactivity to emotional film clips (Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993). In these studies, we used regression models to examine how much variance in reactivity to the film clips was accounted for by the baseline EEG measures after variance associated with prefilm mood was removed. In other words, some portion of the variance in a person's reactivity to a particular film clip might be accounted for by her or his mood just prior to the presentation of the clip. Many factors might influence such phasic shifts in mood. In these studies, we wished to determine how much variance the baseline measures of brain activity accounted for after we removed the variance in baseline mood. We used scales of current mood that were administered just prior to the presentation of the film clips to provide data on prefilm mood and ratings administered just after the film clip that requested subjects to report on their emotion during the clip to provide a measure of their reactivity to the emotional stimulus. We (Wheeler et al., 1993) found that subjects with greater left frontal activation reported more intense positive affect in response to the positive clips, while subjects with greater right frontal activation reported more intense negative affect in response to the negative clips. In this study, we also computed an index of generalized reactivity that consisted of summing the positive and negative affect scores. Frontal asymmetry was unrelated to this generalized reactivity index, again suggesting that these asymmetries are valence specific and do not reflect a more generalized gain or amplification function.

In normal young adults, we have examined some relations between measures of anterior asymmetry and immune function. There are two reasons why we decided to explore this relation. First, Geschwind and his colleagues proposed that laterality and immune function would be related based on common mechanisms during embryogenesis (Geschwind & Galaburda, 1987). They have reported on associations between anomalous handedness patterns and immune disorders (Geschwind & Behan, 1982). Second, there are data from animal studies that suggest dramatically different immune consequences as a function of left- versus right-sided neocortical lesions. Renoux and colleagues (Renoux, Bizière, Re-

noux, & Guillaumin, 1983) have reported that mice with left neocortical lesions show more compromised immune function (e.g., lower natural killer [NK] cell activity) compared to animals given comparable right neocortical lesions. These data, in particular, suggest that asymmetric patterns of activation may be associated with differences in immune function, possibly as a function of the effects of such unilateral lesions on emotional functioning. Unfortunately, assessments of emotional behavior were not made in these animal studies, although, as we have already discussed, unilateral lesions of this type do produce differences in emotional function in both humans (e.g., Robinson, Kubos, Starr, Rao, & Price, 1984) and animals (e.g., Denenberg & Yutzey, 1985). In our first study that examined this issue, we compared extreme left and right frontally activated subjects (selected on the basis of electrophysiological measures as already described) and obtained blood samples to assay for NK cell activity. NK activity has been found to be particularly responsive to emotional state in a variety of prior studies (see, e.g., Kiecolt-Glaser & Glaser, 1991). We (Kang et al., 1991) found that left-activated subjects had greater NK activity than their right-activated counterparts, despite the fact that none of our subjects were clinically depressed or anxious and all were in good health. More recently, we (Davidson, Coe, Donzella, & Ershler, 1994) have replicated this finding and extended it by showing that subjects with greater right-sided anterior activation (particularly in the anterior temporal region) showed a larger decline in NK activity after a naturally occurring stress and after the presentation of a 30-min film clip designed to elicit sadness.

Considered together, our findings in normal young adults suggest that electrophysiological measures of prefrontal and anterior temporal asymmetry are associated with a constellation of behavioral and biological differences related to emotional reactivity and dispositional mood. Subjects with greater left-sided anterior activation report more dispositional positive affect and report more intense positive affect following a positive film clip (after partialling out baseline differences in mood). In addition, such subjects show greater NK activity at rest. Subjects with right-sided anterior activation report less positive and more negative mood compared to their left-activated counterparts. They show more intense negative affect in response to a negative film clip, have less baseline NK activity, and show a greater decline in NK activity following a naturally occurring and an experimentally produced negative event.

An important issue not addressed by these data concerns the mechanisms by which individual differences in anterior asymmetry exert their effects on emotional functioning. In a series of very recent studies, we are beginning to examine this question. We have proposed that the dorsolateral prefrontal cortex is required to implement goal-directed positive affect. As was already described, in this form of positive affect the individual maintains a representation of a goal and moves toward the acquisition of this goal. I have suggested that one consequence of the engagement of dorsolateral prefrontal cortex during this form of behavior is the inhibition of negative affect. Three recent studies from my laboratory provide support for this suggestion. First, Tomarken and Davidson (1994) recently reported that subjects with extreme left frontal activation show a pattern of scores on psychometric measures consistent with repressive defensiveness, a dispositional tendency to inhibit negative affect. Specifically, these subjects score highly on the Marlowe-Crowne (MC) scale and have low scores on measures of anxiety and depression (see Figure 2). Other researchers have demonstrated that high MC scores serve as a protective factor and are associated with decreased lifetime incidence of affective disorders and other manifestations of psychopathology (Lane, Merikangas, Schwartz, Huang, & Prusoff, 1990). Second, we (Davidson, Donzella, & Dottl, 1994) found that subjects with greater left-sided frontal activation show increased suppression of a defensive reflex (the startle)

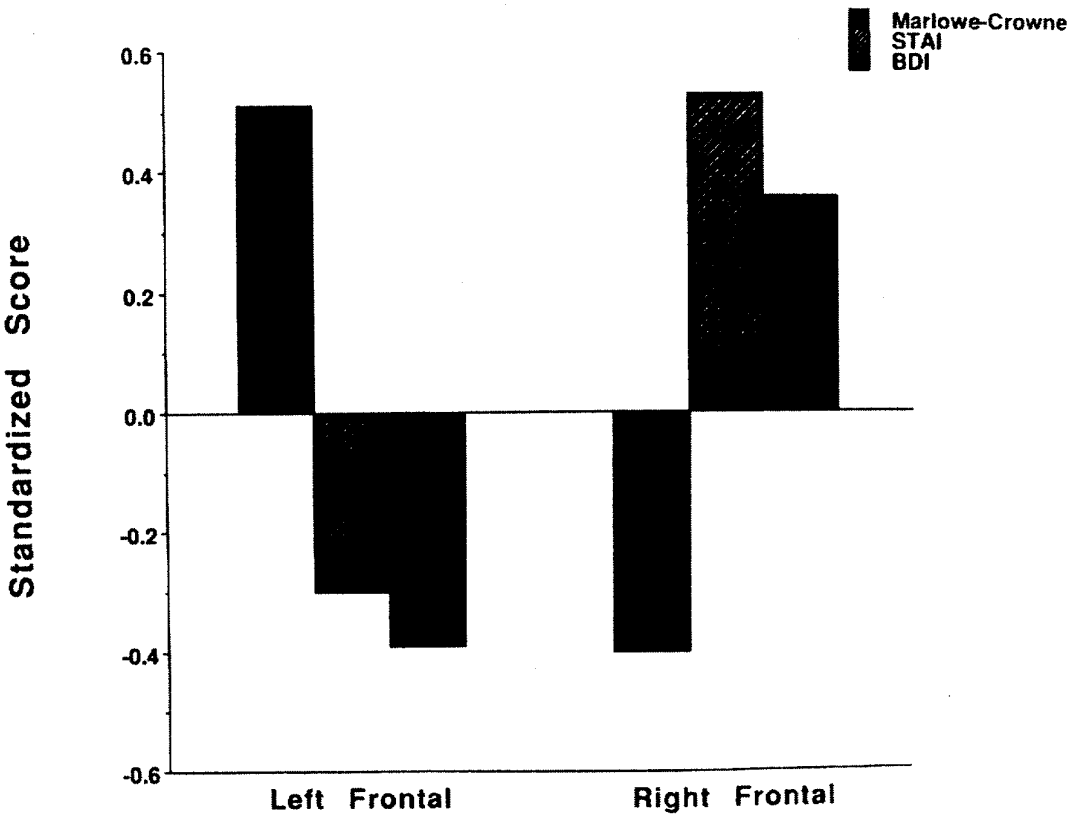

Figure 2. Standardized scores on the Marlowe-Crowne scale, the Beck Depression Inventory (BDI) and the Speilberger State-Trait Anxiety Inventory (STAI; administered in trait form) for subjects with extreme and stable left and right frontal activation. From "Frontal Brain Activation in Repressors and Non-Repressors" by A. J. Tomarken and R. J. Davidson, 1994, *Journal of Abnormal Psychology, 103*, p. 344. Copyright 1994 by the American Psychological Association. Reprinted by permission.

following the presentation of a positive affective stimulus compared to subjects showing more right-sided frontal activation. These data imply that in left frontally activated subjects, exposure to a positive emotional stimulus produces more enduring effects than in subjects with the opposite asymmetry pattern. Finally, we (Davidson, Hugdahl, & Donzella, 1994) studied differences among subjects with differing baseline asymmetries in a simple classical aversive conditioning paradigm. We were particularly interested in this paradigm in light of recent evidence from LeDoux's laboratory (Morgan, Romanski, & LeDoux, 1993) suggesting that lesions of prefrontal cortex in rats interfered with the extinction of a classically conditioned aversive response. We reasoned that in humans it would be the left prefrontal cortex, in particular, that would be associated with differences in the extinction rate of classically conditioned aversive responses. Accordingly, we used a differential auditory conditioning paradigm where neutral tones were paired with an aversive noise. Electrodermal responses served as the dependent measure. We hypothesized that subjects with greater left-sided frontal activation would show faster extinction of the classically conditioned aversive association. For each subject, we computed the slope of the extinction curve for both the CS^+ and the CS^-. We found that subjects with greater baseline left-sided frontal activation showed significantly steeper extinction curves for the CS^+ (after subtracting the slope of the CS^-). These data indicate that left frontally activated subjects are faster at unlearning (extinguishing) a classically conditioned

aversive response compared to their right-activated counterparts.

These three studies together suggest that one mechanism responsible for the affective quality of left prefrontally activated subjects is the inhibition of negative affect. These subjects show more rapid extinction of classically conditioned negative emotional responses, are more likely to show persistent inhibition of a defensive reflex after the presentation of a positive stimulus, and show a dispositional tendency to suppress negative affect. Subjects with left prefrontal activation, therefore, may differ from others primarily in the rapidity with which negative emotion is terminated once it is elicited and not necessarily in the frequency or initial amplitude of such emotion. Additional research is clearly necessary to carefully examine these other possibilities.

We have extended the examination of relations between individual differences in anterior asymmetry and emotion to affective psychopathology. According to our model (Davidson, 1993), decreased left prefrontal activation reflects underactivation of an approach-related system and should therefore decrease an individual's propensity to experience pleasure and to develop a positive engagement with the environment and increase the likelihood of developing depressive symptoms.

Early work in our laboratory (Schaffer, Davidson, & Saron, 1983) compared subclinical depressives with nondepressed controls during resting baselines. This study found that depressives were characterized by increased amounts of alpha activity (i.e., decreased activation) in the left frontal region.

Henriques and Davidson (1991) replicated this study using a group of clinically depressed subjects who met Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) for major depression. These subjects were compared to a group of control subjects who had no history of psychopathology either in themselves or in their first degree relatives. Although Schaffer et al. (1983) had only examined alpha activity in the frontal and parietal regions, Henriques and Davidson (1991) looked at left and right hemisphere activity in six anterior and posterior scalp regions. In addition to power in the alpha band (8–13 Hz), power in the delta (1–4 Hz), theta (4–8 Hz), and beta (13–20 Hz) bands was examined as well as a high-frequency (70–80 Hz) band that presumably reflected muscle or electromyogram (EMG) activity. EEG data were recorded so that three different reference montages could be used in analyzing the data. This approach was adopted in light of the lack of agreement in the literature regarding the appropriateness of different referencing strategies (i.e., Lehmann, 1987). Furthermore, the demonstration of consistency across reference montages would indicate that observed group differences were not a function of the particular reference montage used. This study found that the one region where depressed subjects differed from normal controls was in the patterning of alpha power in the midfrontal region. Depressed subjects had more alpha power in the left frontal region compared to controls. No group difference was observed in right hemisphere alpha power. This pattern of left frontal hypoactivation was consistent across reference montages and was specific to the alpha band. These significant group differences remained after EMG asymmetry had been regressed out, demonstrating that the effects observed were not the result of group differences in muscle activity.

In an effort to gather initial data relevant to the question of whether our findings of baseline prefrontal asymmetry differences between depressed and nondepressed subjects are a function of the *state* of depression or, more consistent with our model, are a *trait* feature of individuals who are vulnerable to depression, we compared previously depressed subjects with control subjects who had never been depressed (Henriques & Davidson, 1990). The previously depressed subjects had been symptom-free for at least 12 months and medication-free for at least 1 month, and they did not differ from never-depressed controls in self-reported

mood at the time of testing. Normothymic depressives differed from controls in the patterning of both anterior and posterior alpha asymmetry. These subjects, just like the currently depressed sample, were characterized by decreased relative left-sided anterior activation. In addition, these subjects had decreased relative right-sided posterior activation. Once again, these significant group differences were observed across recording montage, were specific to the alpha band, and were not the result of any differences in EMG asymmetry.

The model posited at the beginning of this paper was one wherein the levels of activation in the left prefrontal region were reflective of pre-goal attainment positive affect. A consequence of this model is that subjects with less pre-goal attainment positive affect should be less motivated by incentives of reward. We attempted to examine this question in a behavioral study (Henriques, Glowacki, & Davidson, 1994) where we assessed signal detection performance under three conditions: no incentive, reward, and punishment. Rewards and punishments were monetary and were structured such that a more liberal response bias (i.e., responding target more often) would maximize payoffs under both reward and punishment conditions. We tested subclinical depressives, selected on the basis of consistently elevated scores (16 or above at initial testing and 12 or above 8 weeks later) on the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, & Erbaugh, 1961), on this signal detection task and compared their performance to that of normal controls (BDI scores of 2 or less at initial testing and 5 or less 8 weeks later). We used a verbal memory task divided into three conditions (no incentive, reward, and punishment), with the no incentive condition always presented first, followed by the reward and punishment conditions, presented in random order across subjects. Subjects were presented with a series of words in the first phase and then, after a distractor task, they were presented with the words to which they had been previously exposed as well as an equal number of filler items. Their task was to press one button if the word had been previously presented, and another button if the word was new. We found that depressed subjects failed to alter their response bias under the reward incentive compared to the no incentive control condition, while normal subjects adopted a significantly more liberal response bias. The groups did not significantly differ in response to the punishment incentive. These data demonstrate that the goal of attaining increased monetary payoff motivated the nondepressed subjects to adopt a more liberal response bias. The same goal did not change the behavior of depressed subjects compared to their performance under the no incentive condition.

Other recent work from my laboratory indicates that anxiety disorders may be associated with a different pattern of anterior brain function compared to depression. According to the model articulated in the introduction, we would expect that the anterior temporal region, particularly on the right side, should be activated during withdrawal-related emotion and psychopathology. We (Davidson, Henriques, Tomarken, & Marshall, 1994) compared DSM-III-R (American Psychiatric Association, 1987) social phobics to control subjects while they anticipated making a public speech. The control subjects were all accustomed to making public speeches, as they were selected on this basis. We studied the brain activity of these subjects during a period prior to the speech performance while they anticipated making the speech. A tape recording during the anticipation period announced when each 30-s interval had elapsed and indicated the amount of time remaining prior to the speech. The phobics showed a large increase in activation from baseline in the right anterior temporal region during the anticipation period compared to control subjects. Unlike the pattern observed in our studies of depression where the group difference was in the left hemisphere, the effect here was primarily in the right hemisphere, with phobics showing *more* activation compared to controls. These data suggest that the activation of withdrawal-

related emotion in phobics produces a change in anterior brain function different from that seen in depressives and underscores the selective involvement of approach- and withdrawal-related systems in depressive and anxiety disorders, respectively.

As part of our research program on relations between anterior brain function and emotional processes, we have been studying these characteristics in infants and children in the hopes of identifying patterns of brain activity early in life that might predict risk for psychopathology. In recent work, we found that 3-year-old children, selected on the basis of behavioral measures of temperament to be extremely inhibited and shy using criteria similar to those of Kagan and colleagues (Kagan, Resnick, & Snidman, 1988), showed a pattern of frontal brain function that was remarkably similar to our adult depressives (Henriques & Davidson, 1991) and different from an uninhibited and middle group. The difference between groups was primarily in activation of the left frontal region, with the inhibited children showing less activation than the other two groups. The single most robust behavioral difference between the groups is the duration of time that the children stand in close proximity to their mothers during a peer play session with an unfamiliar child of the same sex. During the time the child is proximal to the mother, she or he is not interacting with the peer, nor with the mother, nor is the child playing by her- or himself with toys that are available around the room. Such an individual may be described as having an approach deficit because the salient behavioral feature is a reticence to approach novel or unfamiliar objects and people. Three major questions arise from these findings:

1. To what extent do these early patterns of brain function predict the subsequent development of affective and/or anxiety-related psychopathology once the children reach young adulthood?
2. What is the relative influence of heritable and environmental causes of these early patterns of anterior brain asymmetry?
3. To what extent are these early patterns of brain function plastic (i.e., modifiable)?

Although clear answers are not yet available to any of these questions, some informed speculation is possible based on the extant corpus of animal and human data.

Plasticity in the Face of Stability

Although individual differences in baseline measures of anterior activation asymmetry are relatively stable over time, it is clear that these tonic asymmetries are modulated by a variety of factors. There are short-term phasic influences that can be produced by both psychological as well as pharmacological interventions. For example, among adult subjects, film clips designed to elicit positive or negative affect phasically shift prefrontal and anterior temporal asymmetry, with greater relative left-sided activation observed in response to the positive compared to negative elicitors (Davidson et al., 1990). In infants, both social (e.g., Davidson & Fox, 1982) and nonsocial (Fox & Davidson, 1986) positive and negative stimuli have been used to demonstrate asymmetric shifts in frontal brain electrical activity. These shifts in asymmetry are superimposed on more tonic traitlike individual differences in baseline asymmetry (Davidson & Tomarken, 1989). The range of individual differences is much greater than that produced by the relatively mild laboratory elicitors of emotion that have been used. Other types of procedures have been used to elicit components of emotion, and their effects on anterior EEG asymmetry have been studied. Using muscle-by-muscle instructions to manipulate the face into prototypic expressions, Ekman and Davidson (1993) have found that such procedures produce reliable changes in anterior brain activity, with a smile that had been previously associ-

ated with the felt experience of positive affect producing more left-sided activation than a social smile that did not include the contraction of the eye muscles (orbicularis oculi).

In addition to these behavioral and psychological manipulations, a few studies have examined the effects of certain pharmacological challenges on measures of frontal asymmetry. For example, Mathew, Wilson, and Daniel (1985) used the xenon inhalation technique to compare the effects of an acute dose of diazepam to placebo on regional cerebral blood flow in normal adults. They found that diazepam produced an asymmetric shift in frontal blood flow, with a greater reduction on the right side than the left side. In restrained rhesus monkeys, we (Davidson, Kalin, & Shelton, 1992) used scalp-recorded measures of brain electrical activity to assess possible asymmetric shifts in frontal and parietal scalp regions to an acute dose of diazepam compared to vehicle (i.e., a placebo injection) administered in a separate session. Diazepam produced an increase in relative left-sided frontal activation, with no significant change in parietal asymmetry. Interestingly, Kalin and Shelton (1989) demonstrated that diazepam specifically reduced behavioral inhibition (operationalized as freezing in response to a novel human stimulus) and increased approach behavior in monkeys, an effect consistent with our findings of increased relative left-sided frontal activation.

Baxter and his colleagues (Baxter et al., 1992) have recently reported on an important study that has potentially significant implications for issues that are considered here. Using PET, they examined regional glucose metabolism in patients with obsessive compulsive disorder who were treated either with a drug that has been shown to be effective (fluoxetine) or with a behavioral intervention (exposure and response prevention). They found that both the drug and the behavioral treatment led to comparably significant decreases in glucose metabolism in the head of the caudate nucleus. While they did not report on any asymmetries, this study is important in demonstrating that a successful behavioral intervention produced changes in regional glucose metabolism that were comparable to those produced by a common pharmacological intervention. It is not known whether behavioral and/or pharmacological therapy for depression alters patterns of asymmetry, although several groups are now performing the needed studies.

Each of the studies already described examined only phasic effects. An intervention was made and the immediate effect of the intervention on measures of brain function was examined. These findings clearly indicate that activation asymmetry is not fixed but, rather, is responsive to short-term contextual and pharmacological influences. What is not known is whether the repetitive presentation of particular classes of stimuli, or regular training of a particular sort, or long-term exposure to a particular class of drug can alter patterns of anterior asymmetry in a relatively enduring way. Also needed is a better understanding of the effects of critical periods on organismic susceptibility to such effects.

The importance of early critical periods in modulating the effects of early intervention is clearly illustrated in research on the hormonal influences on behavioral inhibition in rat pups. For example, by 14 days of age, altricial rat pups terminate ongoing behavior and assume defensive postures when threatened. This constellation of behavior may be similar in certain respects to the behavioral inhibition studied in human children (Kagan et al., 1988). If rat pups are adrenalectomized at 10 days of age, they fail to show emergence of inhibited behavior at 14 days. Moreover, daily administration of corticosterone restores the freezing behavior (Takahashi & Rubin, 1993). However, if the corticosterone is administered only on Days 14–17, it is ineffective in potentiating freezing above the level of vehicle-treated rats (Takahashi, in press). These data imply that, at least in rats, the hypothalamic–pituitary–adrenal (HPA) axis is important in the emergence of behavioral inhibition and that interventions made prior to

the emergence of behavioral inhibition may produce long-lasting effects on the expression of this characteristic. They also indicate that there is a very narrow window during which corticosterone is required for the subsequent expression of behavioral inhibition. If this hormone is not present during Days 10–13, then even very high doses (e.g., 12 mg/kg) are ineffective in potentiating freezing if they are given after this critical period (Takahashi, in press). In light of the relation between behavioral inhibition and asymmetric brain function observed in humans, it would be extremely interesting to examine the effects of HPA axis manipulations on the development of asymmetry in rats.

Whether or not similar critical periods exist in human development for the effects of early environmental influences on anterior asymmetries is not known. We do know from other animal studies that prenatal stress can produce large and long-lasting effects on neurotransmitter asymmetries. For example, Fride and Weinstock (1988) found that prenatal stress increases anxious behavior and produced elevated rates of dopamine turnover in the right prefrontal cortex and a reduction in turnover in the left corpus striatum when the offspring were 6 months of age. The authors speculated that their findings may be related to reports in humans of selective activation of right hemisphere anterior regions in anxiety. They concluded their article by explaining,

> To the best of our knowledge, this study yields the first evidence that prenatal environmental manipulation results in long-term changes in cerebral lateralization in the offspring. We suggest that these changes may underlie the increased level of anxiety observed in these prenatally stressed animals. (p. 1064)

A number of researchers have examined the relation between pre- and perinatal stress in humans and motoric lateralization (e.g., handedness). For example, using maternal age as a proxy for increased risk of birth complications, Coren and Porac (1980) reported that maternal age predicted deviations from the normal pattern of dextrality on measures of hand, foot, eye, and ear lateral preferences. However, most direct assessments of relations among prenatal stress, birth complications, and motoric laterality have not found evidence for an association among these variables (e.g., Nachshon & Denno, 1987; Schwartz, 1988).

It is important to underscore the nature of the laterality measure used in these studies. These studies were conducted to evaluate the popular claim that there is an increased frequency of non-right-handedness among populations subjected to early neurological insult. However, lateral motor preferences are not directly related to asymmetries in hemispheric activation of the sort already described. In the studies reviewed from our laboratory, all of the subjects were exclusively right-handed. A wide range of individual differences in anterior activation asymmetry were clearly present despite the consistency in handedness. Similarly, other investigators reported robust individual differences on perceptual measures of laterality among exclusively right-handed samples that reliably predict performance on other measures (e.g., Levy, 1983). These findings suggest that any future attempt to examine relations between pre- and perinatal stress should include measures of activation asymmetry and not simply measures of motoric lateralization.

Greenough and Black (1992) distinguished between experience-expectant and experience-dependent brain plasticity. Experience-expectant mechanisms appear to have evolved in cases where the information to be acquired is common to all young members of a species. Such experiential events play a key role in pruning synapses. Examples of the type of experiential events that Greenough and Black consider within the experience-expectant category include basic sensory input and motor output. Experience-expectant plasticity acts on a substrate of synapse overproduction to sculpt the neuronal machinery as a function of species-typical early environmental input. In humans, it may well be the case that the process of synapse overproduction and re-

finement might occur at an early age in sensory and motor systems, but at a later age for certain cognitive and affective processes. Consistent with this speculation are data of Huttenlocker and his colleagues (Huttenlocker, 1979; Huttenlocker, de Courten, Garey, & Van der Loos, 1982), who found that the density of synapses in human visual cortex peaks at 8–12 months of age and drops rapidly thereafter, whereas synapse loss in the human frontal cortex appears to continue to at least 7 and possibly 14 years of age. Considering the importance of frontal cortex to affect regulation, the fact that synapse pruning in this region continues for so long may imply that affective experience during the formative years of development has an opportunity to mold connections in frontal cortex, which then might endure. Deviations from species-typical patterns of attachment, opportunities for mastery, provision of rewards, and exposure to punishments may interfere with the normal process of synapse pruning in the frontal cortex over the long course of infant and childhood maturation.

The other major form of plasticity, experience-dependent, refers to events that are idiosyncratic for each individual. Experience-dependent processes result in localized synaptic overproduction, followed by deletion. From the research of Greenough and colleagues (Greenough & Black, 1992), it appears that the critical requirement for experience-dependent plasticity is learning and memory formation. Of particular relevance to the central issues considered here, it has been found that lateralized training experiences can produce unilateral structural brain changes. Rats trained to reach for food with the same forelimb everyday showed increases in dendritic branching largely confined to the hemisphere opposite to the trained forelimb (Greenough, Larson, & Withers, 1985). Whether similar asymmetric structural changes might arise as a consequence of exposure to affective experiences that are predominantly under unilateral control is unknown at present, but the motor data suggest that such changes might be possible.

Taken together, the findings from the study of the effects of pre- and perinatal stress on neurotransmitter asymmetries, and the data on experiential shaping of synaptic processes, suggest that early environmental processes can alter brain function and structure and result in enduring changes that have potentially important behavioral consequences. These findings also underscore the complexity of the distal causes of individual differences in prefrontal asymmetry. Stability that is observed among adults on measures of anterior activation asymmetry may arise from a multitude of causes, some of which may be driven by early environmental events that shape a partially plastic brain.

Summary and Conclusions

I began by tracing some of the early work on the effects of unilateral cortical lesions on emotional processes. This work provided an important foundation for modern efforts to understanding the functional neuroanatomical substrates of emotion and affective psychopathology. Next I considered a model of approach- and withdrawal-related emotion and motivation, informed by the brain structures likely to be involved in the different subcomponents of these processes. Two major forms of positive affect were distinguished: pre-goal attainment and post-goal attainment positive affect. Only the former is hypothesized to engage the prefrontal cortex, particularly on the left side. The latter is associated with positive emotions such as contentment and is expected to occur when the prefrontal cortex goes off-line after a desired goal has been achieved. One function of pre-goal attainment positive affect is to inhibit negative affect. Data were presented in the next section of the article that support the notion that individual differences in asymmetric patterns of prefrontal and anterior temporal activation are stable over time and predict important features of affective reactivity. Moreover, subjects with heightened left prefrontal activation show a tendency to inhibit the processing of negative emotional

stimuli and show more rapid extinction of learned negative emotional associations. In addition, such individual differences are related to vulnerability to affective and anxiety disorders. In particular, depressed subjects show decreased activation in the left prefrontal region compared to controls; such differences are also present between remitted depressives and controls, suggesting that the difference in brain function is state-independent. Data were also presented that demonstrated that such individual differences in prefrontal activation are present in young toddlers and are associated with the temperamental dimension of behavioral inhibition. Finally, the issue of plasticity was considered. It was noted that despite the fact that electrophysiological measures of anterior asymmetry are stable over time, there is likely to be considerable plasticity in this system. Short-term environmental and pharmacological influences have been established. Less clear is the extent to which repetitive exposure to such influence would produce more enduring effects. Data from animals that examined the effects of prenatal stress on dopamine asymmetries were discussed. These data indicate that prenatal stress produces asymmetric changes in dopamine turnover, with greater effects in right compared to left prefrontal cortex. These transmitter changes are associated with affective changes in the animals that persist into adulthood. The possible effects of critical periods in moderating the impact of experiential events on brain systems that subserve affect was considered. Based on data showing that the process of synapse pruning continues until at least 7 years of age in human frontal cortex, it is likely that there is an extended period during which affective experience might mold brain function and structure over the course of human development.

In their recent review of the genetic basis of complex human behaviors, Plomin and his colleagues (Plomin, Owen, & McGuffin, 1994) make the important point that genetic studies of human behavioral disorders and dimensions provide the best available evidence for the importance of nonheritable factors. This is so since quantitative genetic studies have established that genetic factors account for a maximum of half the variance in such dimensions or disorders. Ironically, despite the enthusiasm of earlier eras of psychology and psychiatry for environmental determinants of behavior, such causes have proven to be far more elusive and difficult to investigate than genetic factors. When knowledge of brain function, maturation, and plasticity is brought to bear on this question, it might help to focus our efforts to identify those early experiential factors likely to play an important role in producing enduring behavioral consequences that are supported by specific molding of the underlying neural machinery.

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