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## Anterior Cerebral Asymmetry, Affect, and Psychopathology

### Commentary on the Withdrawal-Approach Model

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The relationships between emotion and psychopathology have long been recognized, but continue to routinely defy comprehensive understanding. The two most prevalent psychiatric disorders, depression and anxiety (Regier et al., 1988; Weissman et al., 1988), are characterized by a variety of symptoms that could be described as affective, motivational, or both (e.g., feelings of sadness, nervousness, anhedonia, or disinterest). Furthermore, this affective-motivational dysfunction seems to possess linkages to the clusters of cognitive, behavioral, and somatic dysfunction associated with these disorders. Such a relationship is unsurprising in light of a growing theoretical consensus that: (a) particular psychopathologies represent unique patterns of extreme points on basic dimensions of personality that are independently and normally distributed throughout the population and characterize both normal and pathological individuals (e.g., Cloninger, 1987; Eysenck & Eysenck, 1985; Hirschfeld & Klerman, 1979); (b) the temperamental substrata of personality are themselves products of individual differences in emotional reactivity and dispositional mood, or what Davidson and colleagues have labeled "affective style" (Davidson, 1998a; Davidson & Irwin, 1999; Davidson & Tomarken, 1989). Thus, dysfunction of the neurobehavioral mechanisms responsible for mediating affect can be thought of as the proximal cause of a variety of psychiatric disorders.

In this way, the constellations of cognitive, behavioral, and somatic dysfunction that characterize different psychopathologies may usefully be viewed as secondary to a more central affective-motivational deficit. This is not meant to imply that, for example, the psychomotor retardation associated with certain subtypes of depression is less important than the accompanying depressed mood. Nor is it meant to imply that affective dysfunction is the sole, or even primary, cause of all types of psychopathology or all pathological symptoms. Rather, the value of an affective-motivational model of psychopathology is primarily heuristic, providing a general theoretical framework for the integration of the knowledge amassed by investigators across a broad range of disciplines

into a more comprehensive and coherent understanding of the psychological and neurological mechanisms underlying the etiology and expression of psychopathology.

### Cerebral Asymmetry and the Neurobehavioral Substrates of Affect

#### *A Withdrawal-Approach Model of Affect*

The notion that hemispheric asymmetry plays an important role in the neurobehavioral modulation of emotional expression is an old idea (e.g., Jackson, 1878; Kinsbourne, 1978), but one that has received increasing empirical support in recent years (for reviews, see Heller, 1990, 1993; Leventhal & Tomarken, 1986; Silberman & Weingartner, 1986). The idea that hemispheric asymmetry should be related to psychopathology is a more recent theoretical development that largely stemmed from clinical observations of the patterns of affective dysfunction exhibited by patients with unilateral cortical lesions (for reviews, see Davidson, 1984; Gainotti, 1972, 1989a, 1989b; Kinsbourne & Bemporad, 1984; Silberman & Weingartner, 1986; Wexler, 1980). The most robust finding has been that pathological expressions of negative affect (e.g., crying) are associated with damage to the left hemisphere, whereas positive expressions (e.g., laughing) are associated with right hemisphere damage. This suggests that the substrates of negative affect are located in the right hemisphere, whereas those of positive affect are in the left.<sup>1</sup>

Based on an extensive review of the literature, as well as the results of a number of electroencephalographic (EEG) studies conducted in his own laboratory, Davidson and colleagues (for reviews, see Davidson, 1992, 1993, 1994a, 1994b, 1998b) have proposed a model of asymmetric contributions to the modulation of affect and motivation. This model postulates the existence of two basic affective circuits or systems, the *withdrawal system* and the *approach system*, best described as subcomponents of the conceptual nervous system (Hebb, 1955). The withdrawal system mediates aversive motivation and withdrawal-related negative affect, whereas the approach system mediates appetitive motivation and approach-related positive affect. The withdrawal system is believed to be associated with asymmetric activation<sup>2</sup> of the right anterior region, whereas the approach system is believed to be associated with asymmetric activation of the left anterior region.<sup>3</sup>

Moreover, Davidson has argued that to the extent that aversive (withdrawal-related) or appetitive (approach-related) motivation are constituents of a given affective state, that emotion will be associated with activation of the anterior cerebral regions believed to subserve the functioning of the withdrawal or approach systems. Consistent with other theoretical accounts derived from the investigation of a wide variety of psychological phenomena (e.g., Kagan, Reznik, & Snidman, 1988; Schrierla, 1959; Stellar & Stellar, 1985), the model postulates that "approach and withdrawal are fundamental motivational dimensions which may be found at any level of phylogeny where behavior itself is present" (Davidson, 1992, pp. 126–127). Emotions, therefore, can be characterized as "motivationally tuned states of readiness" (Lang, 1995, p. 373), clus-

ters of action tendencies that systematically shape and define behavior. In this model, affect, the subjective experience and expression of emotional states, is viewed as the product of particular withdrawal- and approach-related motivational states.

Such a motivationally oriented interpretation of affect receives further support from the work of Depue, Krauss, and Spont (1987; see also Collins & Depue, 1992). Based on the work of Tellegen and Watson (e.g., Tellegen, 1985; Watson & Tellegen, 1985), showing that phasic mood is fundamentally organized into two dimensions of negative and positive affect, Depue et al. (1987) have demonstrated that the positive affect dimension is better described as a matrix of energy and appetitive motivation dimensions, consistent with its role as the substrate of approach-related positive affect.

Davidson and colleagues have further argued that individual differences in the tonic level of activation of the withdrawal and approach systems (as indexed by baseline measures of asymmetric anterior activation) predispose individuals to experience more or less withdrawal-related negative or approach-related positive affect, respectively. In other words, while phasic (i.e., state) shifts in both the direction and magnitude of anterior asymmetry in response to emotionally salient stimuli do occur, such transient changes appear to be superimposed upon more trait-like patterns of valence-specific<sup>4</sup> emotional reactivity and self-reported dispositional mood (e.g., Tomarken, Davidson, & Henriques, 1990; Tomarken, Davidson, Wheeler, & Kinney, 1992; Wheeler, Davidson, & Tomarken, 1993). Thus, the proximal cause of affective style, the tendency to respond to affectively salient stimuli in a particular idiosyncratic manner, seems to be related to individual differences in tonic anterior EEG asymmetry. Individuals with greater tonic activation of the left frontal region, for example, are predisposed to react more strongly to positive emotional stimuli and report more dispositional positive affect.

#### *Limitations of the Withdrawal-Approach Model*

While such a model is consistent with a tremendous corpus of data suggesting that affects are organized at the most superordinate level according to their valence (e.g., Diener et al., 1985), it has difficulty explaining several common affective phenomena. First, the model offers only a limited account of the neurobehavioral processes that mediate emotions believed to reflect a state of post-goal attainment positive affect (e.g., amusement, contentment, or tranquility). Davidson (1994a) has speculated that such affects reflect the phenomenological experience of the approach system going off-line after a particular goal has been achieved and should be relatively unrelated to activation of the dorsolateral prefrontal cortex (DLPFC). While such an argument is plausible, given the importance of working memory to goal-directed behavior and the critical role the DLPFC appears to play in working memory (Goldman-Rakic, 1990; Shimamura, 1995; cf. D'Esposito, Ballard, Aguirre & Zahra, 1998), it currently lacks express empirical support.

Second, the model has difficulty accounting for those affects, most notably anger and sadness, that seem to involve either withdrawal- or approach-related motivational components or blends of the two. Sadness, for example, may include an approach component, reflecting the desire to regain a lost object of at-

tachment or a withdrawal component, reflecting the desire to escape the evoked context, depending upon contextual parameters and idiosyncratic appraisal of the eliciting stimulus (Bowlby, 1973; Fox & Davidson, 1984, 1988).

Comprehensive illumination of this class of phenomena is, at least in part, dependent upon an accurate understanding of the neurobehavioral mechanisms governing interaction of the withdrawal and approach systems. If sadness elicited, for example, by maternal separation can include both the desire to escape the event that precipitated the loss (i.e., withdrawal component) and a longing to regain the caregiver's presence (i.e., approach component), then it becomes necessary to know how the systems operate when both are phasically activated. Unfortunately, despite the proliferation of a number of similar neurobiologically based opponent-process models of affective-motivational processes (for reviews, see Fowles, 1993; Lang, 1995), neither the psychological nor the neurological linkages between the systems has been investigated adequately.

An alternative approach is to explore this conundrum from the vantage point of its outcome variables, namely personality and affect. Within the personality literature, there exist three principal models of the interaction between negative and positive affect. Some theorists (e.g., Russell, 1980) have described affect-space using two dimensions, the first a bipolar affective valence dimension, the second a bipolar arousal or "engagement" dimension. Others (e.g., Watson & Tellegen, 1985) have proposed two orthogonal unipolar dimensions of negative and positive affect. Finally, a third camp (e.g., Diener & Emmons, 1984) has suggested that the degree of orthogonality between the two types of affect is temporally dependent. More specifically, state-dependent indices of phasic negative and positive affect should be reciprocally related, whereas state-independent indices of dispositional negative and positive affect should be orthogonal. All three proposals are derived from the factor analysis of self-report measures of mood or of the relations between mood- and affect-relevant words. Unhappily, as is well known, although such methods can establish the number of independent dimensions of variation within a particular dataset (cf. Block, 1995), they are incapable of establishing the "true" rotation of those dimensions, the location bearing the closest resemblance to the empirically identified relations between negative and positive affect. Without additional evidence, it is impossible to know which of the three models is the most accurate rotation of the analytically derived dimensions. Moreover, because each is derived from self-report measures of mood, it is difficult to ascertain the degree to which they accurately reflect the underlying neurobehavioral circuitry.

Davidson and colleagues (for a review, see Davidson, 1994a), as part of an ongoing attempt to delineate the interrelations between withdrawal-related negative and approach-related positive affect more precisely, have performed several studies germane to the issues at hand. Left-prefrontally activated subjects were found to demonstrate more rapid extinction of classically conditioned negative emotional responses (Davidson, Hugdahl, & Donzella, in prep.), enhanced inhibition of the acoustic startle defensive reflex following the presentation of positive affective stimuli (Davidson, Donzella, & Dottl, in prep.), and a predisposition to inhibit negative affect as indexed by the Marlowe-Crowne Social Desirability scale (MC; Crowne & Marlowe, 1964). Taken together, these findings suggest that one possible linkage between the withdrawal and approach systems is the suppression or dampening of withdrawal-related negative affect through activation of the approach system. In other words, it is the rapidity with

which phasically elicited negative affect is inhibited that seems to characterize individuals with dispositional activation of the approach system. Alternatively, it may be the case that phasic arousal of the approach system raises the activation threshold of the withdrawal system, requiring greater stimulation to rise from baseline. Naturally, this raises the question: Is such a relationship unidirectional, or does tonic activation of the withdrawal system have similar consequences? That is, are the two systems, as several theorists have argued (e.g., Gray, 1991; Lang, 1995), mutually inhibitory? The answers to such questions will require further research designed to tease apart the mechanisms governing interrelations between the withdrawal and approach systems.

### Depression, Comorbid Anxiety, and the Withdrawal-Approach Model

#### *An Approach Deficit Model of Depression*

Davidson and colleagues (for reviews see Davidson, 1992, 1993, 1994a, 1994b, 1998a; Davidson & Tomarken, 1989), based on several lines of evidence, have hypothesized that tonic hypoactivation of the approach system (i.e., decreased left frontal activation) is the proximal cause of the deficient appetitive motivation, inability to experience positive affect, and lack of positive engagement with the environment that characterize certain subtypes of depression.

*Clinical and Neurological Evidence* Neurologically intact depressives, especially those diagnosed with melancholic or endogenous depression, often experience a host of symptoms that can be broadly described as a loss of appetitive motivation and an inability to experience positive affect, including: anhedonia, loss of interest in previously pleasurable activities, attenuated appetite and ability to sleep, decreased libido, psychomotor retardation, fatigue, and loss of energy (Akiskal, 1994).

Because the depressive symptomatology that so frequently accompanies major neurologic disease is virtually indistinguishable from that characterizing neurologically intact depressives, these disorders have been fruitfully exploited as model systems for the investigation of affective disorders. As was previously noted,<sup>5</sup> several neurological studies have demonstrated that pathological expressions of negative affect, such as contextually incongruent crying, are associated with lesions of the left hemisphere, particularly its more anterior regions. Moreover, a number of studies have shown that secondary depression, severity of depressive symptomatology, and elevated negative affect are also associated with lesions of the left hemisphere (e.g., Black, 1975; Gasparini, Satz, Heilman, & Coolidge, 1978; Perini & Mendius, 1984; Sackeim et al., 1982).

The studies performed by Mayberg and Robinson are especially suggestive of depression's neuroanatomical underpinnings. About 40% of Huntington's patients (McHugh & Folstein, 1975; Shoulson, 1990) and nearly half of those diagnosed with Parkinson's (Cummings, 1992) suffer from comorbid depressive symptomatology. Mayberg et al. (1992), employing positron emission tomography (PET) to examine regional cerebral glucose metabolism, found significant hypometabolism bilaterally in the orbitofrontal and inferior prefrontal cortices of depressed Huntington's patients, compared to those who were symptom-free.

Paralleling these results, Mayberg et al. (1990) found hypometabolism bilaterally in the caudate and orbital regions of the frontal lobes, as well as in the anterior temporal region, of depressed Parkinson's patients, relative to those that were asymptomatic. Finally, they showed that glucose metabolism in the orbitofrontal region was inversely related to depression scores, consistent with evidence from neurological diagnostic tests indicating that depression is more common in patients with frontal-subcortical circuit dysfunction (Wertmann et al., 1993).

In a similar vein, Robinson and coworkers (Robinson & Price, 1982; Robinson, Kubos, Starr, Rao, & Price, 1984; Starkstein, Robinson, & Price, 1987), using computerized tomography (CT), have demonstrated that the severity of post-stroke depression was positively correlated with the lesion's proximity to the left frontal pole ( $r = 0.92$ ; Robinson et al., 1984) and negatively correlated with its proximity to the right frontal pole. It was also found that patients with lesions in the left frontal region and the left caudate nucleus were much more likely to develop depression than those who had lesions in the homologous right-sided region. Depression was diagnosed in 60% of the patients with left anterior lesions and in 90% of those with left caudate lesions.

The observation that a multitude of neurologic diseases—characterized by anatomically and metabolically similar patterns of pathology—can produce symptom profiles demonstrating a relatively high degree of correspondence, is consistent with the notion of a common final causal pathway to depression. Thus, when viewed together, the results of these studies suggest that dysfunction of an affective-motivational circuit linking anterior, particularly left anterior, cortical regions and subcortical limbic structures plays a pivotal role in the expression of depressive symptomatology.

#### *EEG, Behavioral, and Neuroimaging Evidence*

In a series of EEG studies of depressed individuals, Davidson and colleagues have amassed a variety of evidence to support their approach-deficit model of depression. First, the one region that consistently distinguishes depressed from healthy individuals is the left frontal region: both clinically (Henriques & Davidson, 1991) and subclinically (Davidson, Chapman, & Chapman, 1987; Davidson, Schaffer & Saron, 1985; Schaffer, Davidson, & Saron, 1983) depressed individuals exhibit decreased activation of the left frontal region relative to the homologous right frontal region. This finding has since been replicated by Allen, Iacono, Depue, and Arbisi (1993) with bipolar depressed subjects. Second, consistent with the argument that certain subtypes of depression are related to an appetitive motivation deficit, subclinical depressives were found to be less motivated by incentives of reward in a signal-detection task than non-depressed controls (Henriques, Glowacki, & Davidson, 1994). These two findings, namely that depressives exhibit decreased EEG activation of left anterior regions and are less motivated by appetitive cues, are remarkably concordant with the results of a study performed by Bench, Friston, Brown, Frackowiak, and Dolan (1993) using PET to study regional cerebral blood flow (rCBF) in a group of patients diagnosed with major depression. Bench et al. observed a negative correlation between rCBF in left DLPFC and left angular gyrus and clinical ratings of patients' relative psychomotor retardation and mood disturbance, a finding they have interpreted as a reflecting the impoverished intentional be-

havior and blunted emotional reactivity that frequently characterize major depression.

Finally, normothymic depressives were shown to exhibit decreased left anterior and right posterior activation relative to controls who had never been depressed (Henriques & Davidson, 1990), consistent with the notion that tonic patterns of anterior cerebral asymmetry represent a state-independent psychobiological index of emotional reactivity and dispositional mood (Tomarken, Davidson, & Henriques, 1990; Tomarken, Davidson, Wheeler, & Kinney, 1992). This finding was also replicated by Allen et al. (1993).

*A Stress-Diathesis Conceptualization of Depression* Taken together, these studies suggest that left anterior hypoactivation is a state-independent marker of an individual's vulnerability to develop depression. That is, particular tonic patterns of asymmetric anterior activation predispose individuals to chronically experience greater negative or positive affect, given the requisite stimuli. As applied to psychopathology, this implies that left frontal hypoactivation is not itself a sufficient cause, but rather a diathesis that, in the presence of the appropriate environmental stressors (e.g., Finlay-Jones & Brown, 1981), predisposes individuals to develop depression (Davidson & Tomarken, 1989; Henriques & Davidson, 1991). Such an explicit stress-diathesis formulation receives further support from two additional observations: First, not every patient with left anterior brain lesions expresses depressive symptomatology (e.g., House, Dennis, Warlow, Hawton, & Molyneux, 1990). Second, in EEG studies of neurologically intact subjects, not every individual with hypoactivation of the left frontal region exhibits depressive symptomatology, although they do report more dispositional negative affect (Tomarken, Davidson, Wheeler, & Doss, 1992) and are predisposed to react more intensely to negative affective stimuli (Tomarken et al., 1990; Wheeler et al., 1993). Thus, such individuals are predicted merely to be at greater risk for developing depression.

#### *Limitations and Applications of the Approach-Deficit*

##### *Model of Depression*

*Posterior Cortex and Clinical Heterogeneity* One criticism of such a conceptualization of depression arises from its treatment of the relations between posterior cortical regions and depression. Sinyor, Kaloupek, Becker, Goldenberg, and Coopersmith (1986), for example, found a positive correlation between lesion location and severity of depressive symptomatology in the left hemisphere, consistent with the findings of Robinson et al. (1984). However, they found a curvilinear relationship in the right hemisphere, such that both anterior and posterior lesions were positively correlated with the severity of depressive symptomatology. This relationship was also observed by Robinson and his colleagues, who noted that right posterior lesions were associated with depression. Several other neurological studies have also found an association between depression and damage to right posterior association cortex (e.g., Finset, 1988). And while a number of EEG studies have observed no asymmetries in posterior activation during depressed affective states (e.g., Davidson, 1992), several EEG and PET studies have found asymmetric activity over parietotemporal regions during depressed states (e.g., Davidson et al., 1985, 1987; Davidson & Tomarken, 1989; Post et al., 1987). Moreover, the pattern of parietotemporal asymmetries

found in such studies is robust: depressives who exhibit relative right anterior activation also exhibit relative left posterior activation. That is, the pattern of parietotemporal asymmetries, when it is found at all, is reciprocal to that of the frontal regions.

Heller and colleagues (Heller, 1990, 1993; Heller, Etienne, & Miller, 1995; Heller & Nitschke, 1998) have interpreted such inconsistencies as reflecting the high rate of comorbidity and mixed symptomatology between depression and anxiety (Katon & Roy-Byrne, 1991), especially among the subclinically depressed populations commonly employed in psychological research (Hiller, Zaudig, & Rose, 1989). Based upon the results of a number of neuroimaging (e.g., Buchsbaum et al., 1987; Mathew, Wilson, & Daniel, 1985; Naveteur, Roy, Ovelac, Steinhilg, 1992) and neuropsychological studies (e.g., Banich, Stolar, Heller, & Goldman, 1992; Bruder et al., 1989; Jaeger, Borod, & Peselow, 1987) showing that depressive states are associated with hypoactivation of the right parietotemporal region (i.e., relative left posterior activation), whereas anxious states are associated with hyperactivation of the right parietotemporal region (i.e., relative right posterior activation), Heller et al. concluded that the high degree of variability found in posterior asymmetry patterns among depressives is due largely to the opposing asymmetry patterns represented by depression and anxiety.

In light of the fact that 25% of all individuals who meet the criteria of *Diagnostic and statistical manual of mental disorders*, 3rd ed., rev. (*DSM-III-R*; American Psychiatric Association, 1987) for major depression have a history of panic disorder (Katon & Roy-Byrne, 1991) and over half of all individuals with subclinical symptoms of depression or anxiety exhibit mixed symptomatology (Hiller, Zaudig, & Rose, 1989), it is highly probable that samples of depressed individuals will vary widely in both their frequency and severity of co-occurring anxiety. This heterogeneity produces varying ratios of hypo- and hyperactivating anxiety. This heterogeneity produces varying ratios of hypo- and hyperactivation of right parietotemporal cortex, obscuring the effects of depression upon posterior cortical asymmetry patterns. Such an account also offers a tentative explanation as to why those studies that found significant posterior asymmetries (e.g., Davidson & Tomarken, 1989) generally employed more severely depressed or anxious subjects. To wit, because the degree of symptom co-occurrence is negatively related to symptom severity, such studies are less likely to be confounded by co-occurring hypoactivation (i.e., characteristic of depression) or hyperactivation (i.e., characteristic of anxiety) of the parietotemporal region. Conversely, the opposing activation patterns engendered by mixed symptomatology would tend to suppress one another and, consequently, attenuate the observed posterior hemispheric asymmetry.

**Comorbid Depression and Anxiety** While clinical heterogeneity represents a major methodological concern in its own right, it also begs the related theoretical question: What is the relationship between the withdrawal-approach model and the comorbidity of depression and anxiety? One recent conceptualization of this phenomenon is Clark and Watson's (1991b) tripartite model (see also Clark, Watson, & Mineka, 1994). Their model posits the existence of three factors to account for the patterns of convergent and divergent symptomatology characterizing the two disorders (Swinson & Kirby, 1986). A common distress factor, broadly described as (trait) negative affectivity or neuroticism (NA/N), is hypothesized to mediate the expression of both depression and anxiety, ac-

counting for their high degree of comorbidity and symptom overlap. A depression-specific factor, characterized as low (trait) positive affectivity or extroversional arousal, are believed to underlie the disorders' nosologic independence, especially with more severe symptomatology.

The tripartite model's account of the disorder-specific factors believed to mediate the expression of depression and anxiety is generally consistent with the perspective expounded by Davidson and his colleagues (Clark and Watson view low PA/E as the temperamental core of depression, paralleling the approach-related positive affect deficit proposed by Henriques and Davidson (1991) as the proximal cause of certain subtypes of depression,<sup>6</sup> Clark et al. (1994) have also argued that PA/E is subserved by a neurobehavioral system characterized by increased appetitive motivation, similar to the views of Davidson (e.g., Tomarken, Davidson, Wheeler, & Doss, 1992) and others (e.g., Depue & Iacono, 1989). Specifically, they identify PA/E with Gray's (1982, 1987) behavioral activation system (BAS). Akin to Davidson's approach system, the BAS is an affective-motivational system sensitive to positively valenced stimuli that works to increase nonspecific arousal, attention to and appraisal of appetitive stimuli, and behavioral activation.

The tripartite model's explanation of anxiety as reflecting (trait) hyperarousal of the autonomic nervous system is also consistent with the withdrawal-approach model, albeit in a less direct fashion. Davidson and his colleagues have argued that the withdrawal-related negative affect characterizing certain anxiety disorders reflects tonic hyperactivation of right anterior temporal and possibly right frontal cortex (Henriques & Davidson, 1993; Davidson, Kalin, & Shelton, 1992). Individual differences in tonic activation of this withdrawal system are, in combination with input from the approach system, thought to constitute the neurobehavioral substrate of affective style. Individuals with greater tonic activation are predisposed to react more strongly to negative emotional stimuli, report more dispositional negative affect, and be more vulnerable to the development of anxiety disorders.

Clark et al. (1994), on the other hand, view anxiety as reflecting hyperactivation of the autonomic nervous system. While such a conceptualization is consistent with a wealth of evidence showing an association between heightened physiological arousal and a variety of anxiety disorders (e.g., Clark & Watson, 1991a; Noyes & Holt, 1994), it fails to adequately explain why the dimension is moderately correlated with NA/N. Clark et al. have interpreted these results using Fowles' (1993) synthesis of Gray's (1987) fight-flight system and Barlow's (1988) alarm reaction, which suggests that both are associated with a heightened sensitivity to internal physiological cues. Seen from this perspective, heightened sensitivity to autonomic cues represents the primary anxiety-specific diathesis, paralleling Barlow's suggestion that panic disorder arises when an individual who has experienced panic attacks (i.e., alarm reactions) develops an anxious apprehension about future attacks. Fowles has, in fact, postulated that individuals who possess high trait NA/N are predisposed to develop anxious apprehension. In this way, the tripartite model arranges the two traits hierarchically: NA/N is viewed as an overarching dimension of general reactivity to negative stimuli that increases the likelihood of developing anxiety sensitivity, itself a subordinate, anxiety-specific diathesis. Such a relationship would account for the moderate correlation between the two dimensions.

Thus, anxiety sensitivity seems to represent the personological manifestation of a psychological (i.e., autonomic hyperactivation) vulnerability to the development of anxiety, consistent with Davidson's (1993, 1994a) argument that tonic hyperactivation of the withdrawal system psychological individuals to react more strongly to negative stimuli; anxiety sensitivity also represents a diathesis that, given the requisite environmental stressors, is the proximal cause of certain anxiety disorders. However, the extent to which activation of right anterior temporal cortex indexes anxiety sensitivity, rather than NA/N (i.e., trait sensitivity to negative stimuli) or some other more specific dimension remains unclear. Presently, the results of several EEG studies support only the notion that right anterior activation represents an index sensitive to anxiety, but not depression: activation of this region was found in social phobics (Henriques & Davidson, 1993), but not in depressives (e.g., Henriques & Davidson, 1991). It should be kept in mind, however, that it is improbable that a measure as spatially coarse as regional EEG activation constitutes a disorder-specific index.

On a related note, there still exists a degree of ambiguity as to whether the activity of the right anterior cortex most closely represents fear, anxious apprehension, or both. Barlow (1988; see also Fowles, 1993), in particular, has made the distinction between two types of anxiety: fear and anxiety. Fear, in such a conceptualization, is associated with alarm reactions and, akin to Cannon's (1929) "fight or flight" response (cf. Gray, 1991), is characterized by increased behavioral and cardiovascular activity. Anxiety, however, is characterized by anxious apprehension of aversive outcomes and is associated with increased negative affect, autonomic arousal, and allocation of attentional resources to negative self-evaluative concerns. Anxious apprehension is posited to be the proximal cause of both generalized and panic anxiety disorders. Unfortunately, it is unclear as to whether the sort of laboratory paradigms commonly employed in anxiety research (e.g., asking social phobics to give a public speech) elicit fear, anxiety, or some blend of the two, making it difficult to interpret the significance of particular EEG or neuroimaging studies to models of anxiety disorders.

Additional complications arise from the tripartite model's characterization of NA/N: Clark et al. (1994) have argued that the broad dimension of NA/N acts as a general distress factor mediating the etiology and expression of both depression and anxiety. Thus, NA/N is viewed as the personological substrate of the comorbidity and symptom overlap between the two disorders. Furthermore, in invoking Fowles' (1980, 1987) explication of Gray (1975, 1982, 1987), Clark et al. ally NA/N with Gray's behavioral inhibition system (BIS). An inconsistency arises, however, when identifying NA/N with the BIS and then equating the BIS with Davidson's withdrawal system. While PA/E is clearly related to the approach system, it is unclear how the hierarchically related dimensions of NA/N and autonomic hyperarousal/anxiety sensitivity correspond to the withdrawal system. One hypothesis, given the relative grossness of the regional EEG activation metric, is that NA/N corresponds to activation of the diffuse right anterior regions believed to subserve the withdrawal system, whereas anxiety sensitivity is related to the activity of either a subset of those cortical regions or, perhaps, to the activity of one of the subcortical structures (e.g., the amygdala) believed to play a role in the affective-motivational circuit (Lang, 1995; LeDoux, 1987, 1993). The veracity of such a speculation has yet to be empirically tested.

An alternative conceptualization of comorbidity draws upon Gray's (1991) analysis of the neurobehavioral processes underlying neurotic depression and

the model of impulsivity proposed by Wallace, Newman, and Bachorowski (1991). Gray has posited that the depressive symptomatology characterizing neurotic depression, a subclinical anxiety disorder (cf. Akiskal, 1994), reflects a process of chronic system disinhibition. That is, the depressive symptomatology, reflecting hypoactivation of the BAS, is secondary to the BIS hyperactivation that underlies the primary anxiety disorder.<sup>7</sup> Hyperactivation of the BIS leads, via the reciprocal inhibitory projections linking the two systems (Gray, 1991), to an inhibitory hypoactivation of the BAS and hence is indirectly responsible for the subsequent development of comorbid depression. A similar account can be used to explain the co-occurrence of anxious symptomatology with depressive disorders. To wit, hypoactivation of the BAS, the proximal cause of depression, may lead to a secondary disinhibition of the BIS, precipitating the BIS hyperactivation hypothesized to mediate anxiety.

Such an account is consistent with the withdrawal-approach conceptualization of psychopathology proposed by Davidson and colleagues, especially in light of the clear theoretical parallels between the roles the withdrawal system/BIS and approach system/BAS are posited to play in the development and expression of anxiety and depression, respectively (for reviews, see Davidson, 1994a; Gray, 1991). Nonetheless, it fails to address Clark and her colleagues' assertion that NA/N represents a general distress factor underlying the expression, as well as the frequent co-occurrence, of the two disorders.

In order to address this assertion, it is beneficial to draw upon the model of impulsivity proposed by Wallace et al. (1991). Their conceptualization is derived primarily from the theories of Eysenck (1967) and Gray (1987). Eysenck posited that personality space is best described with two orthogonal dimensions: extraversion (E) and neuroticism (N). E, in this model, is characterized as a dimension of cortical arousal and reflects individual differences in the tonic activity of the ascending reticular activating system (ARAS; Maruzzi & Magoun, 1949), whereas N is characterized as a dimension of emotionality (Eysenck & Eysenck, 1985) and reflects individual differences in reactivity to environmental stimuli.

Gray (1981), however, has argued that E and N do not represent the most parsimonious rotation of the analytically derived axes. He proposed instead two orthogonal dimensions which he labeled anxiety and impulsivity, representing an approximately 45° rotation of the primary Eysenckian dimensions. E is viewed as reflecting the relative strengths of anxiety and impulsivity, whereas N reflects the summation of their absolute strengths. Gray, moreover, has suggested that anxiety and impulsivity are directly related to functioning of the BIS and BAS, respectively. Thus, N reflects the additive strengths of the BIS and BAS, whereas E reflects their relative strengths. In addition to the BIS and BAS, Gray (1987) has postulated a third system, the nonspecific (i.e., valence-independent) arousal system (NAS), conceptually akin to the ARAS. Excitatory inputs from the BIS and BAS project to the NAS, increasing its activity and, consequently, global arousal. Thus, an increase in the activity of either the BIS or BAS will, through excitation of the NAS, enhance the speed and vigor of ongoing behavior.

Wallace et al., like Gray, have suggested that E reflects individual differences in the relative strengths of the BIS and BAS. Extraverts, for example, are more sensitive to positively valenced stimuli, because of their relatively stronger BAS. Thus, E is viewed as a valence-dependent dimension of personality. In

contrast to Gray, however. Wallace et al. argue that N directly reflects the reactivity or lability of the NAS, rather than the additive strengths of the BIS and BAS. Neurotics, therefore, are predisposed to experience greater NAS reactivity and, consequently, faster and more vigorous behavioral responses to a given input from either the BIS or BAS. N, therefore, is a valence-independent dimension. In this way, heightened neuroticism (N) can be viewed as representing a vulnerability to the development of depression, anxiety, or both—consistent with both the tripartite model and Gray's model of comorbidity. Specifically, increased N reflects greater NAS reactivity which, in turn, leads to an exaggeration of normal BIS/BAS-mediated (i.e., withdrawal-approach system-mediated) responses. Thus, while it is perfectly normal for healthy individuals to experience the "blues" occasionally, in neurotics the heightened response strength engendered by that individual's hyperreactive NAS will predispose him or her to experience this negative affect much more strongly, even pathologically.

It is important to note the implications entailed by the argument that E represents the relative strengths of the withdrawal and approach systems. This leads to the prediction that introverts, for example, should exhibit relative right activation. But it says nothing about the hemispheric source of the asymmetry pattern: hypoactivation of the left frontal region (i.e., characteristic of depression) or hyperactivation of the right frontal region (i.e., characteristic of anxiety). Consistent with Clark et al.'s (1994) characterization of N/A/N, such a conceptualization predicts only that neurotic introverts should be (a) characterized by a pattern of relative right EEG activation, and (b) more vulnerable to depression and/or anxiety. Together, the theoretical strands arising from Gray's model of system disinhibition and Wallace et al.'s model of impulsivity help to extend and refine the tripartite model's account of comorbidity.

## Implications and Conclusions

### *Implications and Suggestions for Future Research*

A number of questions emerge from the present discussion of the relative strengths and limitations of the withdrawal-approach model. First, the ability of the model to describe or account for given affective states is predicated upon the argument that certain affects are composed of or driven by more elementary, withdrawal- and/or approach-oriented motivational states. At the present time, however, the evidence for such a fundamental postulate remains scanty. While the intimate ties linking emotion to motivation have long been appreciated, it would be of great interest to know exactly how the two are related. Is emotion, for example, the phenomenological experience of more basic motivational drives? Research designed to tease apart such relations would also be applicable to several of the issues previously explicated. For example, what are the neurobehavioral mechanisms responsible for mediating those affective states, most notably anger and sadness, that seem to include both withdrawal and approach components? Similarly, if left anterior EEG activation is hypothesized to constitute an index of pre-goal attainment positive affect (Davidson, 1994a), what are the relations between pre- and post-goal attainment-modulated motivational state and affect? That is, how are appetitive and consummatory motivational

states (cf. Sherrington, 1906; Woodworth, 1930) differentially related to particular affective states?

Second, although a number of theorists (e.g., Gray, 1991) have suggested that the twin withdrawal and approach components function as a reciprocally inhibitory opponent-process system (Solomon & Corbit, 1974), little is known about the mechanisms governing either phasic or chronic interactions of the withdrawal and approach systems. Research designed to investigate this issue would be broadly relevant to the understanding of a multitude of enigmatic phenomena, including mixed-motivation affective states, co-occurring depression and anxiety, and bipolar depressive/cyclothymic disorders.

Third, it is commonly acknowledged that nearly all regions of neocortex are highly interconnected to form layers of local and distributed networks in which particular, discrete regions of cortex subserve parallel multimodal processing functions (Mesulam, 1990). It has been suggested that the dorsolateral prefrontal cortex (DLPFC), for example, plays a role in a variety of tasks related to the temporary maintenance of spatial, serial, and conditional associative information (Cohen et al., 1994; Kolb, 1990). Damage to DLPFC has been linked to a variety of cognitive, motivational, and affective deficits, including deficits in creativity, mental flexibility, planning, temporal coding, metamemory, judgment, insight, attention, perseveration, confidence, inhibitory control, and novelty detection (Damasio, 1994; Knight & Grabowecy, 1995). And yet, previously few studies have investigated the relationships between the affective-motivational role and other, more purely cognitive functions ascribed to the DLPFC and other neocortical structures implicated by the withdrawal-approach model.

Similarly, there exists the need to better integrate the results of the many studies (Aggleton, 1992; Gray, 1991; Lang, 1995; LeDoux, 1987) focusing on subcortical structures with the studies (exemplified by the work of Davidson and his co-workers) that have focused on cortical regions. Both regions seem to play critical roles in the modulation of affect. Unfortunately, neither group has adequately addressed the circuitry presumably governing interactions between the two regions. Future conceptualizations of affective-motivational circuitry should attempt to bind the two theoretical clusters more closely (cf. Drevets, 1999).

Fourth, it has become increasingly clear in recent years that major depressive disorder is a nosologically, symptomatically, and quite likely etiologically heterogeneous category encompassing a constellation of related, but distinct subtypes of depression (Andreasen, Grove, & Maurer, 1980). But until recently, too few investigators have adequately controlled for this heterogeneity. Instead, the use of *DSM-IV* (American Psychiatric Association, 1994) diagnostic criteria or Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978)—criteria designed to maximize diagnostic reliability rather than nosologic validity—was deemed sufficient. Moreover, although the nature of the relationship between mild and clinically significant depression is highly complex (Gotlib, 1984), many depression studies continue to use mildly dyshythmic college students for the sake of convenience. These recruiting practices have had a tremendous impact upon the field, compounding the inconsistency of the depression literature. Future studies of depression should structure their recruiting and screening practices to better identify specific subtypes of depression. One approach that seems useful is that undertaken by Bench et al. (1992, 1993) in their PET studies of depression. Patients diagnosed with major depressive disorder

were recruited from local acute psychiatric services. Multivariate analysis of patients' symptom ratings was then employed to establish dimensions of depressive symptomatology that were correlated with observed patterns of regional brain activity without requiring an *a priori* categorization of subgroups (cf. Nurcombe, 1992).

### Conclusions

Fowles (1993) has suggested that the following are the minimum elements for a theory of psychopathology: genes, enzymes, neurotransmitter systems, environment, behavior and psychological processes, and psychopathology.

Although this commentary has only explored a small portion of the larger realm encompassed by psychopathology research, it is important to consider for a moment a few of the issues affecting the domain as a whole. Fowles's suggestion offers an elegant analog to one of the most germane of these issues, that of integration. Just as a complete theory of psychopathology requires the integration of multiple levels of analysis, so too must the study of psychopathology begin to integrate more fully the information derived both from different subdomains within the fields of psychology and psychiatry and from other academic disciplines.

The ambitious research program conducted by Davidson and his colleagues exemplifies this sort of syncretic approach. In the past decade, they have conducted a multifaceted effort, employing a variety of different populations (including young children and monkeys) and methods (such as PET and functional magnetic resonance imaging) to tease apart the relations between individual differences in asymmetric patterns of anterior cerebral electrical activity, affective style, and psychopathology. This work led Davidson and his collaborators to propose a biphasic model of cerebral modulation of affect and motivation. A withdrawal-related negative affect system, associated with increased activation of right anterior regions, and an approach-related positive affect system, associated with activation of left anterior regions, form the core of their model. As applied to psychopathology, the model posits that hypoactivation of the approach system is the proximal cause of the appetitive motivation deficits, the ability to experience positive affect, and lack of positive engagement with the environment that characterize certain subtypes of depression. While not without its limitations, the approach-deficit model has made significant contributions to our understanding of the neurobehavioral substrata mediating the expression of certain subtypes of depression. Notably, it has served as a framework for the continued investigation of this constellation of disorders and the integration of a wide variety of knowledge from other domains.

Block (1995), in his analysis of the five-factor approach to personality description, has written that:

once the parameters that define the personality system of a generic individual have been conceptually posited and empirically identified, these parameters become the essential, nonarbitrary, overarching variables or concepts for a personality of interindividual differences. The differences between individuals would then be understood as due to the different specific values these parameters take in different individual personality systems. (p. 210)

Psychopathologists would do well to consider Block's argument. Fundamental understanding of depression will require intimate understanding of the parameters governing its functional neuroanatomical substrata, the dimensions defining its many clinical manifestations, and its interrelations with the affective, motivational, and cognitive processes defining normative personality and behavior.

### Notes

1. Such a hypothesis is based on the implicit assumption that focal brain lesions act as deactivating forces in the region in which they are located (Burke et al., 1982; Heller, 1990; Takeuchi et al., 1986). However, such an assumption has been criticized by a number of commentators (e.g., Nadeau & Crosson, 1995) as overly simplistic in light of current models of neuronal organization (Damasio, 1989; Goldman-Rakic, 1988a, 1988b; Hopman & Davidson, 1994), which emphasize the dynamic, multifocal nature of processing and posit that higher order cognitive functions reflect the ensemble actions of interconnected local networks (Edelman & Mountcastle, 1977; Mesulam, 1990, 1998). Ablation of a particular region may precipitate a cascade of excitatory or inhibitory, local or diffuse metabolic consequences. For example, fibers of passage connecting wholly independent regions may be severed, or destruction may lead to disinhibition of an area receiving inhibitory projections from the ablated region. Careful consideration of the difficulties involved in precisely localizing the functional significance of focal lesions should, therefore, inform interpretation of the conclusions drawn from such studies.

2. Activation asymmetries refer to the extent to which a hemisphere or region is differentially activated relative to the homologous region of the opposite hemisphere. Activation, as measured by EEG, is typically defined operationally in terms of suppressed activity in the alpha band (8–13 Hz). Alpha is widely regarded as an inverse index of activation (Pivik et al., 1993; Shagass, 1972). Thus, suppressed alpha activity (i.e., greater EEG desynchronization) is indicative of increased activation and serves as an aggregate measure of local neuronal activity.

3. The withdrawal-approach model primarily emphasizes the contributions of the anterior cortex, linking activation of right anterior regions (e.g., right frontal, right prefrontal, and right anterior temporal cortex) and left anterior regions (e.g., left dorsolateral prefrontal cortex) to functioning of the withdrawal and approach systems, respectively. Nonetheless, it also critically implicates a number of subcortical (e.g., amygdala, basal ganglia, hypothalamus), central cortical (e.g., motor and premotor cortex), and posterior cortical (e.g., somatosensory cortex) structures, consistent with other bivalence theories of emotion, motivation, and/or psychopathology (e.g., Gray, 1987, 1991; Konorski, 1967; Mackintosh, 1974; for reviews, see Davidson & Irwin, 1999; Fowles, 1993; Lang, 1995; LeDoux, 1987, 1995; Panksepp, 1989, 1998; Rolls, 1995, 1999).

4. Because of the ambiguity with which the term "emotional reactivity" is frequently employed in the literature, the term "valence-specific" (cf. Watson & Tellegen, 1985) is adopted to distinguish affective reactivity that is dependent upon the valence of an eliciting stimulus from the concept of valence-independent reactivity (e.g., Larsen et al., 1986; see also Lang, 1995), that is, generalized reactivity that is unrelated to an elicitor's affective valence (see also Tomarken, Davidson, Wheeler, & Doss, 1992; Wheeler et al., 1993).

5. The interested reader should be aware that a substantial corpus of knowledge bears testament to the continuing investigation of the relationships between EEG measures of asymmetric cerebral electrophysiological activity and



psychopathology (e.g., see the volumes by Cutting, 1990; Fior-Henry & Gruzelier, 1983; Gainotti & Caltagirone, 1989; Kinsbourne, 1988; Takahasi et al., 1987). At the heart of this endeavor is an attempt to understand the nature of the causal relationship between individual differences in asymmetric hemispheric activation and the patterns of affective-motivational dysfunction that characterize particular forms of psychopathology.

6. The correspondence between the two models becomes even more apparent if one considers that, although Clark et al. (1994) endorse the notion that PA/E is fundamentally an affective dimension (p. 107), their argument that pure markers of PA (e.g., energetic, assertive, bold) are indicative of strong engagement with tasks or the environment, clearly acknowledges the dimension's intimacies to motivation. These PA markers are, moreover, conceptually related to the sort of positive affects that Davidson (1994a) has suggested arise in the context of approaching desired goals.

7. Comorbid depression and anxiety, it should be noted, can be interpreted in either categorical or dimensional terms. Neurotic depression, for example, is described by Gray (1991) as "depression with a strong admixture of anxiety and occurring in individuals with a neurotic introvert personality" (p. 300). Thus, it is possible to view the disorder as either the expression of depression secondary to anxiety (i.e., a categorical description) or as a blend of depressive and anxious symptomatology with the anxious symptoms being more severe or prominent (i.e., a dimensional description).

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## Cognitive Functioning in Depression

### Nature and Origins

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Of all the psychiatric disorders, depression is by far the most common. Each year, more than 100 million people worldwide develop clinically recognizable depression. During the course of a lifetime, it is estimated that between 8% and 20% of the general population will experience at least one clinically significant episode of depression (Kessler et al., 1994), and that approximately twice as many women than men will be affected by the disorder (Blehar & Oren, 1995; Klerman & Weissman, 1992). Moreover, for a significant proportion of these individuals, the depressive episode will result in death by suicide (Hirschfeld & Goodwin, 1988) or other causes (cf. Murphy, Monson, Olivier, Sobol, & Leighton, 1987). Depression is also a recurrent disorder, with more than 80% of depressed patients experiencing more than one episode over the course of their lives (Belsher & Costello, 1988; Keller, 1985). More specifically, investigators have reported that more than 50% of depressed patients relapse within two years of recovery (cf. Keller & Shapiro, 1981; Kovacs et al., 1981), and data from the NIMH Collaborative Study indicate that individuals with three or more previous episodes of depression may have a relapse rate as high as 40% within only 12 to 15 weeks after recovery (Keller et al., 1992; Mueller et al., 1996). Finally, depressive episodes are fundamentally self-limiting, with approximately 70% of individuals recovering within 40 weeks after the onset of the episode (Coryell & Winokur, 1992; Lewinsohn, Hoberman, Teri, Hautzinger, 1985).

The term "depression" covers a wide range of emotional states that range in severity from normal, everyday moods of sadness, to psychotic episodes with increased risk of suicide. The current diagnostic system in North America, the *Diagnostic and statistical manual of mental disorders (DSM-IV)*, American Psychiatric Association, 1994), divides depression, or mood disorders, into depressive disorders and bipolar disorders. A diagnosis of depressive disorder, the focus of this chapter, requires one or more periods of clinically significant depression without a history of either manic or hypomanic episodes. Depressive disorders are characterized by at least a 2-week period of depressed mood or a