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The Puzzle of Regional Brain Activity in Depression and Anxiety: The Importance of Subtypes and Comorbidity

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The literature on brain activity in depression and anxiety is reviewed with an emphasis on highlighting discrepancies and inconsistencies. In particular, anterior and posterior asymmetries have been reported for both depression and anxiety, but the magnitude and direction of these asymmetries has been variable. We propose that by identifying subtypes of depression and anxiety some of these inconsistencies can be explained. In addition, we review evidence suggesting that issues of comorbidity are important to consider in attempting to account for regional brain activity in depression and anxiety.

INTRODUCTION

A fundamental assumption in cognitive neuroscience is that various regions of the brain perform different roles in the organisation of human behaviour. It is also assumed that most tasks require multiple cognitive operations, each of which depends on a set of neural computations localised to some region(s) of the brain. Thus, it follows that most activities involve a set of brain regions that are recruited by the particular information processing and behavioural demands of the task. In addition, the neural computations involved are viewed as components or subroutines that contribute to, but do not constitute, the final output (i.e. there is no "grandmother cell" or "Wisconsin card sort area"; Petersen, Corbetta, Miezin, & Shulman, 1994). Rather, these elementary processing mechanisms can be called upon by a variety of tasks, and the degree to which they are activated will depend on the unique characteristics of the task. Metaphorically

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speaking, behaviour, like a symphony, is the output of an orchestra of neurones. Each region of the brain, like each section of the orchestra, has a particular role to play and a particular manner in which it affects the overall composition. To understand the making of a symphony, we must identify the component parts.

Emotion, like many cognitive processes, is not a unidimensional construct. Rather, the term subsumes a variety of distinct phenomena, including physiological events (e.g. changes in heart rate or skin conductance), feeling state, and modes of information processing. Thus, emotion is unlikely to "live" in some specific location in the brain; instead, various brain regions are likely to be engaged in different aspects of it. It is therefore crucial that brain activity in emotion be examined in the light of a thorough understanding of the multiple processes and brain regions involved. The degree to which we can disentangle the various subcomponents of the emotional phenomena we are investigating determines the degree to which we can discern the precise neural mechanisms of importance.

In this article, we will address the issues of depression and anxiety from the foregoing perspective. We will emphasise the argument that different subcomponents of the symptomatology of affective and anxiety disorders are associated with distinct regions of the brain. The degree to which these subcomponents are conflated, or co-occur, will obscure our ability to identify the neural mechanisms associated with particular disorders. Furthermore, the more we can be specific about the quality or nature of the symptomatology, the more we are likely to be able to specify the critical brain mechanisms.

In turn, a better understanding of the neural mechanisms involved can inform our understanding of the symptoms of depression and anxiety. For example, if right posterior regions of the brain prove to be dysfunctional in depression, we might expect that depressed people would have difficulty processing narrative information, a task that has been shown to rely, in part, on this area of the brain (Heller & Nitschke, 1997). Because narrative information processing is likely to play an important role in many therapeutic interventions, the significance of a deficit in this area is clear.

Our approach is exemplified by a neuropsychological model developed by Heller (1986, 1990, 1993a,b) in which psychological theories of emotion were used to decompose emotional states into two components, valence and arousal. This model integrates the dimensional circumplex theory of emotion (based primarily on self-report; for a review, see Larson & Diener, 1992) with neuropsychological data on cognitive, emotional, and autonomic functioning during different affective states. Based on evidence from electroencephalographic (EEG), blood flow, and lesion studies, the model posits that the valence dimension (pleasant, unpleasant) is dependent on functions of the anterior regions. Bias toward a particular valence pole

is associated with the relative activity level of the left and right hemispheres. When the left frontal region is active relative to the right, affective valence is pleasant, whereas when the right frontal region is active relative to the left, affective valence is unpleasant. The association of valence with asymmetric activity of the anterior regions has been extensively studied (for reviews, see Davidson, 1992a,b; Heller, 1990) and will be further reviewed in the course of this article.

In contrast, the arousal dimension (or activation dimension: Larsen & Diener, 1992), is posited to depend on right parietotemporal regions of the brain. More activity in this region is associated with higher self-reported arousal, whereas less activity is associated with lower self-reported arousal. This aspect of the model was based on theoretical work by numerous authors (e.g. Heilman, Schwartz, & Watson, 1978; Levy, Heller, Banich, & Burton, 1983; Tucker, 1981) suggesting a special role for the right hemisphere in emotion-related arousal functions. The arousal component of Heller's model derives empirical support from numerous additional studies examining both brain-damaged patients and normal subjects (for reviews, see Gainotti, Caltagirone, & Zoccolotti, 1993; Wittling, 1995).

To briefly review this evidence, self-reports of emotion-related arousal and the right hemisphere have been investigated directly by Heller, Nitschke, and Lindsay (1997b). Greater emphasis on right hemisphere processing, as reflected in a left hemispatial bias on a free-vision task of face processing, was associated with higher levels of self-reported arousal on several indices derived from the Profile of Mood States (an emotional adjective checklist). Self-reported arousal has also been shown to be associated with a number of autonomic functions, particularly skin conductance (Greenwald, Cook, & Lang, 1989; Lang, Greenwald Bradly, & Hamm, 1993). In turn, numerous studies have suggested a link between the right hemisphere and skin conductance; right brain-damaged patients have consistently been found to display reduced skin conductance responses to emotional stimuli (Caltagirone, Zoccolotti, Originale, Daniele, & Mammucari, 1989; Heilman, Schwartz, & Watson, 1978; Morrow, Vrtunski, Kim, & Boller, 1981; Myslobodsky & Horesh, 1978; Valenstein & Heilman, 1984; Zoccolotti, Caltagirone, Benedetti, & Gainotti, 1986; Zoccolotti, Scabini, & Violani, 1982). Compatible with these results, there is considerable evidence for greater autonomic conditioning when conditioned emotional stimuli are presented to the right versus the left hemisphere (Dawson & Schell, 1982; Johnsen & Hugdahl, 1991, 1993). There is also evidence that cardiovascular functions associated with emotional responses are more dependent on the right than on the left hemisphere (Caltagirone et al., 1989; Hugdahl, Franzon, Andersson, & Walldebo, 1983; Wittling, 1990; Zoccolotti et al., 1986).

At the time of its conception, Heller's model attempted to address a number of conflicts in the literature. Which hemisphere was involved in emotion, and in what manner, was a matter of much debate. Based on evidence that the right hemisphere was specialised to process emotional information, some researchers were arguing that all emotional functions were dependent on the right hemisphere. Representative of this perspective, Levy et al. (1983) had obtained behavioural evidence on tasks associated with parieto-temporal functions that led us to conclude that individuals displaying relatively reduced right hemisphere activation were predisposed to unpleasant emotions, whereas individuals displaying enhanced right hemisphere activation were predisposed to pleasant emotions. Based on these findings, we posited that reduced activation of the right hemisphere was associated with depression. This hypothesis was supported by evidence that depressed people display deficits in cognitive functions associated with the right hemisphere on neuropsychological tests and in lateralised tachistoscopic paradigms (for reviews, see Heller, 1990, 1993a,b; Tucker, 1981).

In direct contrast, EEG studies indicated that compared to the left hemisphere, right hemisphere activation was increased in depressed mood states, particularly for anterior regions (for a review, see Davidson, 1984). When mood was euthymic, however, activation of the right hemisphere was decreased relative to the left hemisphere. These results built on a set of observations, systematically described by Gainotti (1972), noting very different emotional behaviours in people with right versus left brain damage. Left hemisphere damage was associated with the so-called "catastrophic reaction", in which patients were described to be emotionally volatile, and especially prone to depression and crying. In contrast, right hemisphere damage was observed to be frequently accompanied by a "euphoric" or "indifference" reaction. Similar emotional responses have been described in patients undergoing the WADA or sodium amytal test. Injections of sodium amytal that deactivate the left hemisphere are associated with the "catastrophic" reaction, whereas those that deactivate the right hemisphere are associated with the "indifference/euphoria" reaction (e.g. Lee, Loring, Meador, Flanigin, & Brooks, 1988).

The EEG and lesion studies inspired what have been referred to as "valence" theories (for a review, see Borod, 1993). In one variant of this type of theory, the left hemisphere was thought to be specialised for pleasant affect, and the right hemisphere was thought to be specialised for unpleasant affect (e.g. Sackeim et al., 1982). To account for the lesion data, it was assumed that brain damage immobilises or diminishes the functioning of the damaged hemisphere, and that the behaviour observed reflects the functioning of the intact hemisphere more or less on its own.

In another variant of a valence theory, Tucker (1981) concluded that unpleasant and pleasant emotions were associated with the left and right hemispheres, respectively, a reversal of the valence theory described earlier. Here, the lesion data were explained by arguing that the observed behaviour was not a function of the intact hemisphere but rather reflected emotional processes of the subcortical areas on the damaged side that were released from cortical inhibition because of the lesion. The EEG data would be explained by assuming that increased anterior activity on one side or the other would inhibit the affect associated with the corresponding ipsilateral subcortical region (unpleasant for the left, pleasant for the right). By this reasoning, it follows that the affective effects of a lateralised subcortical lesion should be opposite to those of a cortical lesion (e.g. a lesion to left subcortical structures should be associated with a suppression of activity in this area, leading to a decrease in unpleasant affect). However, several studies have found left anterior subcortical lesions to be associated with depression (for a review, see Liotti & Tucker, 1995).

In attempting to account for the co-occurrence in depression of increased activation in right anterior regions and deficits on cognitive tasks specialised to the right hemisphere, Tucker (1981) argued that frontal regions have been traditionally viewed as having inhibitory regulatory effects on posterior regions. By distinguishing valence from arousal as components of emotion and localising these dimensions to anterior and posterior regions of the brain, respectively, Heller's (1986, 1990) model also emphasised a caudal distinction. However, the model has additional explanatory power. Although inhibitory mechanisms of the anterior regions may well be playing a role in affective regulation (also see Tomarken & Keener, this Issue), the concept of a (relatively) independent arousal dimension associated with the posterior right hemisphere allows us to model the patterns of brain activity associated with all the emotions as represented on the circumplex. Indeed, the patterns of activity that have been reported for depression and anxiety cannot be fully accounted for by invoking an inhibitory mechanism. For example, if the inhibitory function of the right anterior region is the driving force behind right posterior activity in different affective states, we would expect anxiety (which, like depression, is often accompanied by increased right anterior activity) to be similarly accompanied by decreased right posterior activity. However, the evidence suggests that anxiety is often associated with increased activity in this region (as reviewed later). Thus, by positing an independent arousal dimension, Heller's model provides an explanation for the patterns of brain activity that have been observed for anxiety as well as depression.

Tucker and colleagues have furthermore emphasised the important role of cortical-subcortical interactions in producing the asymmetries in cortical activity. Heller's model does not address the mechanisms by which the

asymmetries associated with affective valence are generated; indeed, it could well be the case that the relationship between activity in the anterior regions and valence is mediated largely via interaction with subcortical structures. Furthermore, inhibitory mechanisms may be important in this regard.

Note that the approach we are emphasising in this article is compatible with Davidson and colleagues' attempts to decompose emotional states according to the degree that they involve approach versus withdrawal behaviours (Davidson, 1992; Davidson & Tomarken, 1989; Tomarken & Keener, this Issue; see also Kinsbourne, 1988). These authors have argued that approach and withdrawal are the fundamental behavioural substrates associated with affective valence. However, this theoretical formulation clearly emphasises the anterior cortical asymmetries associated with pleasant/unpleasant valence. Although Davidson has addressed posterior asymmetries in his work (e.g. Davidson, Schaffer & Saron, 1985; Davidson, 1992a), the approach-withdrawal model does not focus on the patterns of posterior brain activity that have been documented for depression and anxiety. Thus, considering the arousal dimension in addition to the approach-withdrawal distinction may address the data for the posterior regions more comprehensively.

The present article has several goals. We will highlight persistent and emerging discrepancies in the field of brain function in depression and anxiety and suggest that turning to the psychological literature on the specific symptomatology and comorbidity of these disorders can help us resolve at least some of them. In the process, we will revisit Heller's model of emotion with a critical look at how well it has been able to account for the wealth of recent findings in the field. Some modifications to this model will be proposed, and continuing questions will be explicated.

REGIONAL BRAIN ACTIVITY

Anterior and posterior asymmetries in cortical activity are often, but not always, reported in depression and anxiety. As a result, it has been difficult to identify precisely the patterns of brain activity that are important. In the sections following, we highlight the discrepancies in the findings for anterior and posterior asymmetries. We then discuss possible causes for these discrepancies, and suggest ways to disentangle the results.

Depression

Anterior asymmetries for EEG alpha have often been found in studies of depression (e.g. Allen, Iacono, Depue, & Arbisi, 1993; Henriques & Davidson, 1990, 1991; Schaffer, Davidson, & Saron, 1983). Across these

studies, depression has been associated with more right than left anterior activity. Numerous positron emission tomography (PET) studies have also reported less left anterior activity (e.g. Baxter et al., 1985, 1989; Bench et al, 1992; Bench, Friston, Brown, Frackowiak, & Dolan, 1993; George et al., 1994; Martinot et al., 1990), which is consistent with the EEG findings earlier. However, other studies have reported findings in the opposite direction for depression (Drevets et al., 1992) and sad mood (George et al., 1995). Null effects for depression have also been found (e.g. Nitschke, Heller, Etienne, & Miller, 1995; Tomarken & Davidson, 1994).

The findings for the parieto-temporal regons have been even more variable. In EEG and blood flow studies that report positive findings, depression is typically associated with less right posterior activity (e.g. Flor-Henry, 1979; Henriques & Davidson, 1990; Post et al., 1987; Uytdenhoef et al., 1983). Numerous studies, however, report no effects for this region of the brain (for a review, see Davidson & Tomarken, 1989).

Reports of reduced right parieto-temporal activity, although not always present, are consistent with neuropsychological studies often indicating impaired or suppressed right hemisphere function in depressed people. On neuropsychological tasks thought to depend on right parietotemporal functioning, depressed people have often been found to display decrements in performance (e.g. Berndt & Berndt, 1980; Flor-Henry, 1976; Goldstein, Filskov, Weaver, & Ives, 1977; Gruzelier, Seymour, Wilson, Jolley & Hirsch, 1988; Kronfol, Hamsher, Digre, & Waziri, 1978). Similar findings for sad mood in nondepressed people have also been reported for right hemisphere tasks (Tucker, Stenslie, Roth, & Shearer, 1981).

Studies that have directed information to one or the other hemisphere using lateralised paradigms, such as dichotic listening or visual half-field presentation, have also found specific deficits for the right hemisphere in depressed people (for a review, see Bruder, 1995). Left-ear decrements or absent left-ear (right hemisphere) advantages have been reported for depression on nonverbal dichotic listening tasks (e.g. Bruder et al., 1989). Similarly, left visual field (right hemisphere) deficits in reaction time and accuracy for nonverbal stimuli have been reported for depressed people (Bruder et al., 1989; Liotti, Sava, Rizzolati, & Caffarra, 1991). Comparable results have also been obtained in studies of nondepressed people who undergo mood inductions (Banich, Stolar, Heller & Goldman, 1992; Ladavas, Nicoletti, Umilta, & Rizzolatti, 1984): Reaction time and accuracy for the right hemisphere are selectively impaired in sad moods.

On the Chimeric Faces Task (CFT), a free-vision task of face processing that typically elicits a left hemispatial bias suggesting greater right hemisphere activation, Jaeger, Borod, and Peselow (1987) found smaller left hemispatial biases for depressed patients than nonpsychiatric controls. Using the same task, Heller, Etienne, and Miller (1995) reported that

high-depressed participants had smaller left hemispatial biases than low-depressed participants. Due to the nature of the CFT, hemispatial biases are nonspecific as to whether they reflect a decrease in activity for the contralateral hemisphere, or an increase in activity for the ipsilateral hemisphere (i.e. a reduction in the magnitude of the left hemispatial bias could reflect either reduced right hemisphere or increased left hemisphere activity). However, based on the evidence (reviewed earlier) for selective deficits in performance on right hemisphere tasks, relatively poor performance for the left-visual field on tachistoscopic tasks, and reduced EEG activity for right posterior regions, the most likely interpretation of the CFT findings is that they reflect diminished right posterior activity.

In summary, although anterior asymmetries have often been reported in depression, the more common finding of higher left than right activation is not invariably found. Furthermore, there is a significant discrepancy between the number of studies that have reported parieto-temporal asymmetries in activation, which have been relatively few, and the number of studies that have reported deficits in right hemisphere information processing, which have been many. Also worthy of note is whether studies of clinical depression, psychometrically defined depression, and sad mood are addressing the same phenomenon. The number of consistencies across these populations in the physiological literature reviewed here suggests some commonality; on the other hand, the inconsistencies could be in part due to the heterogeneity between the samples studied.

Anxiety

Research on brain activity in anxious states has also been plagued by inconsistencies. Again, although anterior and posterior asymmetries have been reported, no consistent pattern has emerged. Studies of multisite EEG and regional cerebral blood flow (rCBF) using xenon-133 or PET have reported right hemisphere, left hemisphere, and bilateral increases in activity during anxiety (for a review, see Heller, Nitschke, Etienne, & Miller, 1997a). Other studies have found no differences in brain activity (Gur et al., 1988; Mountz et al., 1989; Nordhal et al., 1990; Tomarken & Davidson, 1994).

Having comprehensively reviewed this literature elsewhere (Heller et al., 1997a), we will provide an overview of those studies reporting differential hemispheric involvement in anxiety. A subset of these suggest an asymmetry in favour of right hemisphere activation in various regions (frontal, lateral prefrontal, precentral frontal, anterior temporal, parietal, occipital, and parahippocampal). Heightened right hemisphere activity has been reported for panic disorder patients (Reiman, Raichle, Butler, Herscovitch, & Robins, 1984), panic disorder patients experiencing a sodium

lactate-induced panic attack (Stewart, Devous, Rush, Lane, & Bonte, 1988), generalised anxiety disorder (GAD) patients during an anxiety-stimulating task (Wu et al., 1991), psychometrically defined high-anxious participants immediately following arterial and venous catheterisation and again after completion of the PET scans (Reivich, Gur, & Alavi, 1983), and social phobics prior to making a public speech (Davidson, Marshall, Tomarken, & Henriques, submitted). Consistent with this pattern, anti-anxiety medication was found to reduce the rate of glucose metabolism in the right hemisphere, especially for the occipital and frontal regions, for patients with GAD (Buchsbaum et al., 1987). Similarly, in a population of nonpsychiatric volunteers, those administered diazepam intravenously showed maximal decreases in rCBF in the right frontal area, whereas those injected with a placebo showed no rCBF changes (Mathew, Wilson, & Daniel, 1985).

Regional brain activity can also be inferred from performance on tasks that depend on particular brain regions. On the CFT, Heller et al. (1995) reported that high-anxious participants had larger left hemispatial biases than low-anxious participants, suggested to reflect greater right posterior activity. Similarly, on a neuropsychological test battery, panic disorder patients performed less well than normal controls on left, but not right hemisphere tasks (Yeudall et al., 1983). Data obtained from a series of studies using behavioural measures to examine right versus left hemisphere function during an experimental condition producing transient (i.e. state) anxiety (Tucker, Antes, Stenslie, & Barnhardt, 1978; Tucker, Roth, Arneson, & Buckingham, 1977; Tyler & Tucker, 1982) are also consistent with an interpretation of greater right than left hemisphere activity in anxiety (Heller et al., 1995).

However, when subjects were classified according to trait anxiety, Tucker and colleagues (Tucker et al., 1978; Tyler & Tucker, 1982) interpreted the results as strongly suggestive of greater left than right hemisphere activity. This interpretation is consistent with reports of numerous other labs finding increased left hemisphere activity associated with anxiety in various cortical and subcortical regions (orbital frontal, inferior frontal, anterior cingulate, caudate, putamen, and thalamus). Heightened left hemisphere activity has been found in obsessive-compulsive disorder (OCD) patients (Baxter et al., 1987; Swedo et al., 1989), GAD patients (Buchsbaum et al., 1985; Wu et al., 1991), and students classified as "worriers" on the basis of self-reports when asked to "worry about a specific topic of personal concern" (Carter, Johnson, & Borkovec, 1986).

In summary, some findings for anxiety indicate increased right hemisphere activation, whereas others indicate increased left hemisphere activation. Indeed, it may be the case that they could co-occur, which could

account for the findings of bilateral increases, or no asymmetries. In the meantime, we are lacking a model to explain these discrepancies.

ACCOUNTING FOR INCONSISTENCIES IN BRAIN ACTIVITY

We are thus confronted with inconsistent results with regard to regional brain activity in both depression and anxiety. In previous work, we have argued that in order to resolve these discrepancies, it is helpful to turn to the psychological literature on symptomatology in depression and anxiety. In the sections that follow, we make some general observations that apply to both depression and anxiety before focusing on each more exclusively.

In addressing the inconsistencies for the blood flow findings, several concerns about the literature are worthy of note. First, several of the most frequently cited studies in this literature sampled a restricted set of brain regions (e.g. Reiman et al., 1984; Reivich et al., 1983). Furthermore, the regions of interest were not consistent from one study to the next. Second, statistical procedures employing multiple *t*-tests rather than repeated-measures ANOVAs are questionable, especially with regard to drawing conclusions about hemispheric differences. Third, although some studies examined selected diagnostic groups (e.g. major depressive disorder, OCD, panic disorder, GAD), most treated depression or anxiety as a unitary construct and did not consider that different types of each might be associated with different patterns of brain activity. Moreover, with the exception of recent OCD studies, most did not take into account the degree of comorbidity with depression or anxiety, which may be critical in determining the patterns of brain activity that occur (Heller et al., 1995; Tucker, 1988).

As emphasised by Davidson, Tomarken, and colleagues (Davidson, 1993; Tomarken, Davidson, Wheeler, & Doss, 1992; Tomarken, Davidson, Wheeler, & Kinney, 1992), there are a number of methodological approaches that need to be considered when asymmetric patterns of EEG activity do not emerge. Some of these considerations are relevant to the design of blood flow studies as well. One issue is that of stability (i.e. the extent to which brain activity reflects a stable individual pattern). This can be addressed by obtaining a sufficient number of baseline samples as well as test-retest data. For example, Tomarken et al. (1992) found that only participants with a stable pattern of anterior asymmetry across two measurement occasions showed an association between left frontal hypoactivation and more dispositional negative affect, as measured by the PANAS.

It is also important to note that for the most part, EEG studies have examined resting, or baseline activity. Davidson (1993) has pointed out

that baseline levels of frontal activation asymmetry may reflect individual tendencies toward a valenced affective response, but this relationship may not be observed in the absence of a specific environmental elicitor. Thus, he emphasises the need to examine the relationship between individual differences in patterns of asymmetry and affective response to emotionally challenging tasks. As applied to the pattern of posterior findings, these considerations suggest the possibility that more robust differences in posterior brain activity might be yielded by studies measuring brain activity while participants perform tasks for which depressed people show decrements. Additional methodological approaches highlighted by Davidson and colleagues, such as the use of extreme groups and classification of participants according to the affect measures as opposed to the brain asymmetry measures, would also be useful in future studies of brain activity.

A number of other possible explanations for the failure to find consistent decreases in parieto-temporal activity during depression have been proposed (Heller, 1990, 1993b). One of these explanations focused on the severity of the depression. This supposition was based on the observation that posterior asymmetries were more likely to be reported when depression was relatively severe. Heller suggested that under less extreme affective conditions, task-induced activity predominates, masking the affect-induced activity. More recently, Heller et al. (1995) suggested that severity *per se* is not the issue; rather, because the comorbidity with anxiety decreases as severity of depression increases (Hiller, Zaudig, & Rose, 1989), the opposing effects of anxiety on posterior brain activity diminishes.

Heller (1993b) also suggested that the inconsistencies in the depression and anxiety literatures may be due to significant differences in regional brain activity that covary more strongly with dispositional characteristics associated with emotional functioning (e.g. extraversion) than with situationally induced emotions. Several studies have reported perceptual (Berenbaum & Williams, 1994; Heller & Nisenson, 1993) and EEG (Nitschke et al., 1994) asymmetries for extraversion. Nitschke et al. also found that extraversion moderated the relationship between anxiety and EEG activity across both frontal, central, and parietal regions. For anxious participants, high extraversion was associated with less activity (more alpha), whereas for nonanxious (and nondepressed) controls, high extraversion was associated with more activity (less alpha). These two sets of findings, albeit preliminary, provide evidence for the need to acknowledge regional differences in brain function for personality characteristics, such as extraversion (for a review, see Nitschke, Heller, & Miller, in prep.), and point to the possible significance of personality in understanding regional brain activity in affective and anxiety disorders.

Subtypes of Depression and Anxiety

Another promising avenue for elucidating the discrepancies reported in the literature for both depression and anxiety is the analysis of subtypes.

Depression. Many distinctions for depression have been proposed over the years, including, most notably, bipolar versus unipolar, endogenous versus exogenous, and neurotic versus reactive. The current *Diagnostic and statistical manual of mental disorders–fourth edition* (DSMIV; APA, 1994) subdivides unipolar depression into major depressive disorder and dysthymic disorder and provides further specificity with criteria for severity and for psychotic, melancholic, catatonic, or atypical features.

Perhaps the most useful distinction in physiological research on depression has been the comparison of melancholic to nonmelancholic depression. The defining feature of melancholic depression is anhedonia, which is the inability to experience pleasure. Current consensus, as indicated by the DSMIV (APA, 1994) suggests that melancholia is most strongly characterised by a loss of pleasure in all activities and a lack of responsivity to pleasurable stimuli. Many other symptoms may be shared by both melancholic and nonmelancholic depression, including depressed mood, disturbances in eating and sleeping patterns, low self-esteem, inability to concentrate, psychomotor retardation, fatigue, indecisiveness, feelings of guilt, and thoughts about death. There is current controversy over whether melancholic depression is qualitatively different from nonmelancholic depression, with some authors arguing that the primary distinction is one of severity (Zimmerman, Coryell, & Pfohl, 1986). Nonetheless, neuropsychological and neurophysiological studies have been consistent in demonstrating differences between melancholic and nonmelancholic depression.

In a comprehensive series of studies, Bruder has shown that perceptual asymmetries differ for different subtypes of depression (for a review, see Bruder, 1995). On a perceptual asymmetry task, melancholic patients showed an abnormally large right ear (left hemisphere) advantage for a dichotic syllables task, but no left ear (right hemisphere) advantage for a complex tone task (Bruder, 1995). The lack of a left ear advantage was due to poor left ear accuracy, consistent with other studies demonstrating right hemisphere deficits in depressed people. However, nonmelancholic depressed patients did not differ from normal controls on either test. Along these lines, in a PET study of melancholic depression, Bench et al. (1992) reported less activity in the left dorsolateral prefrontal cortex compared to nondepressed controls. Note that these data could be consistent with either a qualitative or a quantitative distinction between melancholic and nonmelancholic depression. However, other data may be more consistent with a qualitative difference between the two types of depression. For example,

Davidson, Larson, and Abercrombie (1995) reported that depression severity in melancholic subjects was predicted by the extent to which activation was decreased in the left lateral prefrontal region. In contrast, among nonmelancholics, depression severity was predicted by the extent to which activation was increased in the right medial prefrontal area.

Davidson et al.'s (1995) data have implications for theories regarding the relationship between pleasant/unpleasant affect and anterior regions of the brain. Research on the psychological characteristics of depression and anxiety has suggested that lack of positive affect (or, more precisely, activated pleasant affect; Larsen & Diener, 1992) is unique to depression (Clark & Watson, 1991). Indeed, in designing a questionnaire to measure both general and specific components of depression and anxiety, Watson and colleagues (Watson, 1995a,b) developed a specific depression scale that primarily measures anhedonia. Because anhedonia is a fundamental characteristic of melancholia, it seems reasonable to assume that decreased pleasant affect would accompany this type of depression. If so, Heller's model, which predicts less left than right anterior activity for decreased pleasant affect, is completely consistent with the available data.

However, Davidson et al.'s (1995) data suggests the possibility that affective valence may depend less on the relative balance of activation between the left and right anterior regions and more on specific systems associated with each hemisphere. Whereas melancholic depression is characterised by decreased pleasant affect, depression without melancholic features may be better characterised by increased unpleasant affect. Following this line of reasoning, Heller's model, which in its current form argues for a link between anterior asymmetry and the valence dimension, would not distinguish between melancholic and nonmelancholic depression. If affective valence depends more on specific systems associated with each hemisphere, as Davidson et al.'s data suggest, Heller's model may need to be expanded to reflect the unique contributions of the left and right hemispheres to pleasant/unpleasant affect. For example, it might be more accurate to link the left anterior region with the activated pleasant affect (i.e. positive affect) octant of the circumplex model of emotion, and the right anterior region with the activated unpleasant affect (i.e. negative affect) octant (see Larson & Diener, 1992).

Because few studies have specifically examined the full range of potential affective descriptors in relation to patterns of brain activity, these issues remain to be resolved. In most research, only isolated portions of the circumplex have been sampled. For example, because positive and negative affect as measured by the PANAS provide information regarding only two of the four quadrants in the circumplex model, studies that do not collect data regarding the other two quadrants cannot shed light on how well they might have accounted for patterns of brain activity.

Anxiety. As reviewed earlier, studies that examine regional brain activity in anxiety are even more plagued by inconsistencies than studies of depression. In keeping with the theme of this article, we have argued that by decomposing anxiety into subtypes on the basis of the psychological literature, we can potentially resolve some of these discrepancies.

In previous work, we have suggested that it may be important to consider the type of anxiety that is being examined (Heller et al., 1995, 1997a). In particular, we argued that regional brain activity might be different for anxious arousal (e.g. panic) and anxious apprehension (e.g. worry), types of anxiety that appear to differ significantly in psychological and physiological characteristics (e.g. Barlow, 1988, 1991; Eysenck 1957; Klein, 1987; Watson et al., 1995b). Anxious arousal has been described by Watson et al. as being distinguished by symptoms of physiological hyperarousal and somatic tension. Panic attacks and high-stress states would fall into this category. In contrast, anxious apprehension involves worry and is characterised by verbal rumination, typically about future events. This type of anxiety would be characteristic of obsessive-compulsiveness, generalised anxiety states, and trait anxiety (as identified by self-reports of anxious apprehension and worry on various questionnaires). As noted by Heller et al. (1997a), the two kinds of anxiety are not mutually exclusive. Extreme degrees of anxious apprehension (e.g. being worried or fearful about the future) may prompt experiences of anxious arousal (e.g. somatic symptoms and exaggerated physiological responses to stressful events).

We have argued that when the literature on brain activity in anxiety is reviewed in the light of this distinction between anxious arousal and anxious apprehension, most of the studies reporting greater right hemisphere activity have either studied panic attacks (e.g. Reiman et al., 1984) or high-stress situations likely to entail anxious arousal (e.g. Tucker et al., 1977). On the other hand, studies indicating greater left hemisphere activity (primarily anterior) have examined OCD (e.g. Baxter et al., 1987), GAD (Wu et al., 1991), or questionnaire-defined trait anxiety indexing anxious apprehension (e.g. Tucker et al., 1978). Indeed, as mentioned earlier, studies have highlighted various regions in both hemispheres. As a result, it is difficult to pinpoint a particular region that is clearly a focal point in anxiety. Nonetheless, the data do suggest that right hemisphere regions emerge as particularly salient in some types of anxiety (i.e. anxious arousal), whereas left hemisphere regions emerge as particularly salient in other types of anxiety (i.e. anxious apprehension).

In a direct test of this hypothesis (Heller et al., 1997a), we selected participants on the basis of self-reported trait anxiety using a measure indexing anxious apprehension in a between-subjects design. We then manipulated anxious arousal on a within-subjects basis. Specifically, we contrasted brain activity (EEG alpha) during rest periods to brain activity

during a task in which participants listened to emotional narratives designed to elicit anxious arousal (i.e. fear and sad narratives that had previously received unpleasant valence and high arousal ratings).

For frontal activity, group differences were unaffected by the narratives. Anxious participants showed a larger asymmetry in favour of the left hemisphere than controls during the rest and listen periods of all narrative types as well as for eight minutes of resting baseline preceding the narrative task. Examination of the data indicated that the increased asymmetry was primarily due to a decrease in right hemisphere activity for the anxious participants. Nonetheless, the increase in magnitude of the asymmetry favouring the left hemisphere found for anxious participants is consistent with the studies reviewed earlier that reported or inferred relatively greater left than right anterior activity in anxious subjects classified on the basis of worry or trait anxiety (e.g. Carter et al., 1986; Tucker et al., 1978; Tyler & Tucker, 1982). Our frontal data suggest that it will be important to investigate whether anxious apprehension is best characterised by the magnitude of the asymmetry favouring the left hemisphere or by the level of left hemisphere activity in isolation.

In contrast, the parietal data supported our prediction regarding the association of anxious arousal with greater right hemisphere activity. When listening to the fear and sad narratives, anxious participants showed a selective increase in right parietal activity that was not demonstrated by controls. The right parietal effect, however, was not obtained for neutral and happy narratives that had previously received pleasant valence and low arousal ratings. These findings are consistent with those studies that have reported or inferred greater right hemisphere activity during anxious states characterised by panic and stress-inducing conditions (e.g. Reiman et al., 1984; Stewart et al., 1988; Tucker et al., 1977).

An important question here has to do with the discrepancies in frontal asymmetries that have been reported. Like others (e.g. Baxter et al., 1987; Gur et al., 1988; Wu et al., 1991), we did not find heightened right anterior activity in anxiety. However, a number of other studies have (e.g. Davidson et al., 1996; Reivich et al., 1983; Tomarken & Davidson, 1994). As discussed earlier, we have previously argued that anterior regions are uniquely involved in the valence dimension of emotion, with pleasant affect associated with greater left activity and unpleasant affect associated with greater right activity (e.g. Heller, 1990). Therefore, we would expect heightened right anterior activity in an anxious group only if they differed from controls on measures indexing affective valence. In our recent study, the nondepressed anxious group did not differ from controls on either the GBI Dysthymia scale or the PANAS PA and NA scales.

It may also be important to measure the level of anxious apprehension in the sample studied. For example, Tomarken and Davidson (1994) found

that with Marlowe–Crowne scores controlled, trait anxiety failed to predict frontal asymmetry. However, their groups were divided according to a median split.

In summary, our results directly support the proposed distinction between anxious apprehension and anxious arousal as types of anxiety that may account for significant variance in patterns of brain activity. They suggest, furthermore, that Heller's model should be refined to reflect the likelihood that parietal activation will covary with anxious arousal, but not with anxious apprehension. If these distinctions are accurate, we would expect to observe increases in right parietotemporal activity only under conditions when anxiety is accompanied by increased arousal.

Thus, in homodynamic and EEG studies, a failure to find increased right posterior activity in anxiety is not surprising, as variations in anxious arousal are likely to be large. Some individuals may experience anxious arousal frequently, especially those with disorders more characteristic of anxious arousal such as panic disorder, phobias, or post-traumatic stress disorder. Others, although apprehensive, may rarely experience anxious arousal. In addition, the situation may vary in the degree to which it elicits anxious arousal. Being forced to give a speech is likely to induce a great deal of anxious arousal in social phobics; thus, we would have predicted a significant increase in right parietal activity, precisely as found by Davidson et al. (submitted). Note that this effect was only found during the Anticipation condition; not during baseline, Planning, or after the speech. During the Anticipation condition, subjects listened while a voice announced, every 30 seconds for three minutes, the time remaining before they would be given a topic and allowed to plan for their speech. Presumably, this period is the most stressful and the most likely to result in anxious arousal. Indeed, the correlation between heart rate acceleration to the Anticipation condition and the increase in state anxiety was significant.

More recently, Nitschke, Heller, Imig, and Miller (submitted) have attempted to identify anxious arousal and anxious apprehension using questionnaires. Data from 783 students for a battery of anxiety and depression questionnaires provided strong support for the anxiety distinction proposed here, at least on a psychological level of analysis. The Mood and Anxiety Symptom Questionnaire-Anxious Arousal scale (MASQ; Watson et al., 1995a,b) was chosen as a measure of anxious arousal, whereas the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990; Molina & Borkovec, 1994) was included as a measure of anxious apprehension. The correlation between the two scales (r = .20) was much lower than those involving the other more general scales of anxiety included in the study (MASQ-General Anxiety scale, Beck Anxiety Inventory, and the State-Trait Anxiety Inventory-Trait scale, ranging from r = .47 to r = .65). These results further support the

argument that anxious arousal and anxious apprehension are distinct anxiety states.

However, new questions are highlighted by this distinction between anxious arousal and anxious apprehension, particularly in the light of Heller's model. If anxious apprehension is associated with left anterior activity, the overall pattern of regional brain activity appears to be identical to the brain activity associated with pleasant emotional states (i.e. more left than right anterior activity). However, anxious apprehension might be expected to fall in the portion of the circumplex model of emotion associated with activated unpleasant affect (as suggested by adjectives such as fearful, nervous, jittery, anxious). Below, we suggest a number of theoretical possibilities for resolving this apparent discrepancy, all of which remain to be examined empirically.

In general, it will be important to clarify the degree to which anxious apprehension is in fact characterised by unpleasant versus pleasant valence, as well as high versus low arousal. In addition, it may be helpful to consider these anterior asymmetries from the approach-withdrawal framework employed by Davidson (1992a,b; Davidson & Tomarken, 1989). Under conditions where anxious apprehension leads to approach tendencies, one might expect an asymmetry in favour of the left anterior region. In contrast, when anxious apprehension is associated with withdrawal tendencies (perhaps as anxious arousal increases), an asymmetry may emerge in favour of the right anterior region. Conceivably, the degree to which anxious apprehension is characterised by approach versus withdrawal tendencies would depend on the degree of stress and discomfort involved, the person's coping style, and other factors. With regard to valence, we would predict that anxious apprehension characterised by approach tendencies would be accompanied by relatively pleasant affect. Anxious apprehension accompanied by withdrawal tendencies, in contrast, would be accompanied by relatively unpleasant affect.

It is also possible that instead of a direct link between anxious apprehension and approach behaviour, they share more fundamental characteristics associated with left anterior functions. For example, one might argue that they both involve sequential thinking, and the development of hierarchically structured plans focusing on future concerns (for a review of relevant left anterior functions, see Tomarken & Keener, this Issue).

Another important issue has to do with the nature of the asymmetric pattern of activity. As reviewed earlier, we found that the asymmetry in favour of the left hemisphere for participants classified on the basis of trait anxiety was due to a relative decrease in right hemisphere activity. Thus, the left frontal region of the anxious participants was not significantly more active than that of controls. It will therefore be important to examine the possibility that absolute activity of the left anterior region plays a more

important role in the modulation of valence (e.g. Davidson et al., 1995) than of anxious apprehension.

Another possibility is that independent left anterior systems are associated with anxious apprehension versus pleasant affect. Liotti and Tucker (1995) review theories that there may be multiple functionally segregated parallel frontal cortico-striato-thalamic circuits, some associated with motor functions, some with set shifting and behavioural inhibition, and some with emotional information processing and hedonic responsivity to stimuli. Possibly, one of these circuits reflects activation associated with pleasant affect, and another reflects activation associated with anxious apprehension and/or approach. Different neurotransmitter systems could be involved. More precise methods of localisation would therefore be necessary to distinguish the unique brain activity associated with each of these psychological/behavioural phenomena.

Comorbidity of Depression and Anxiety

In considering the issue of decomposing emotional states with regard to the symptomatology in affective and anxiety disorders, we have previously argued that issues of comorbidity of depression and anxiety are crucial (Heller et al., 1995). A review of the literature reveals that rates of comorbidity are extremely high (Alloy, Kelly, Mineka, & Clements, 1990; Heller et al., 1995; Hiller et al., 1989; Katon & Roy-Byrne, 1991). Even in our very recent work (Nitschke et al., submitted) using the MASQ, a measure designed by Watson and colleagues to avoid symptom overlap in the measurement of anxiety and depression (Watson et al., 1995a,b), comorbidity was fairly pronounced in a large college student sample. The MASQ Anxious Arousal (AA) and Anhedonic Depression (AD) scales were used as measures of those constructs, and the PSWQ provided the measure of anxious apprehension. Of the 125 (out of 783) participants scoring above the 80th percentile on at least one of the three scales of interest and below the 50th percentile on any where the 80th percentile cut-off was not met, fully 50% demonstrated comorbidity by scoring above the 80th percentile on at least two of the scales. This rate of comorbidity emerged despite the low correlations found between the three scales (MASQ AA and MASQ AD, $r = .20$; MASQ AA and PSWQ, $r = .20$; MASQ AD and PSWQ, $r = .36$), relative to the correlations found for the other more general measures of depression including the MASQ General Mixed, General Depression and General Anxiety scales, Beck Depression Inventory, Beck Anxiety Inventory, General Behaviour Inventory-Dysthymia scale, and the State-Trait Anxiety Inventory-Trait scale (ranging from $r = .47$ to $r = .76$).

Because at least some studies have found opposite patterns of activity for the right posterior region during depression versus during anxiety (i.e.

anxious arousal), we reasoned that the failure to distinguish carefully between the two could lead, in part, to the inconsistent findings in the literature for that region of the brain. Furthermore, the overlap between depression and anxiety decreases as the severity of the disorder (major depression or panic disorder) increases (Hiller et al., 1989). It would thus be less likely that anxiety and depression would be confounded from a neuropsychological perspective in more severe cases, which is when parieto-temporal differences between depressed and nondepressed people are most likely to emerge (Davidson & Tomarken, 1989).

As mentioned earlier, Heller et al. (1995) examined college students classified as either depressed, anxious or both. It emerged that depression, as expected, was associated with reduced right hemisphere activity, as measured by the CFT. In direct contrast, anxiety was associated with increased right hemisphere activity. These results are consistent with the predictions made by Heller's model for depression and anxiety. Furthermore, they highlight the probability that studies failing to distinguish depression and anxiety, particularly in less-distressed populations, are likely to find the divergent patterns of brain activity obscured.

The inconsistencies for anterior regions in studies of depression and anxiety might also be explained by an understanding of comorbidity. For example, if a nonmelancholic depressed sample also has high levels of anxious apprehension, the increase in right anterior activity associated with such depression might be matched by an increase in left anterior activity associated with anxious apprehension, resulting in a pattern of asymmetry looking identical to a nondepressed, nonanxious control sample. Melancholia and anxious apprehension appear to be associated with opposite patterns of activity in the left anterior region, which might serve to cancel each other out, conceivably resulting in a "normal" level of left anterior activity.

CONCLUSION AND QUESTIONS FOR FUTURE RESEARCH

We have reviewed the literature on depression and anxiety with an eye to highlighting the inconsistencies that have been reported in activity and involvement of different brain regions. We argued that many of these inconsistencies may be resolved by turning to the psychological literature on emotion, depression, and anxiety, as a guide to decomposing complex emotional states into subcomponents. In the process, we considered Heller's model in the light of recent research and refinements in our theoretical position. We suggested that it is important to be clear that our predictions for the right parieto-temporal region are specific to anxious arousal. We also suggested that it may be necessary to modify the model to reflect the

potentially dual nature of the anterior systems associated with valence. To address this possibility, we have recommended that future studies sample the full range of affective descriptors on the circumplex model of emotion when examining the relations between affective states and brain activity and function. Despite these refinements, the fundamental tenets of the model continue to be consistent with emerging evidence in depression and anxiety. Anterior regions of the brain consistently emerge as important in affective valence, whereas the right parieto-temporal region is important in arousal. The model therefore remains a useful guide to theory and research.

Two related questions can be raised with regard to the brain mechanisms in emotion. A fundamental issue has to do with the question as to why the observed asymmetries are associated with affective valence. In particular, we do not know precisely why higher left than right anterior activation is associated with pleasant affect, or why higher right than left activation is associated with unpleasant affect. As relative activation of various brain regions has emerged as a critical component of different affective states, earlier perspectives have shifted from right versus left hemisphere specialisation for affect to differential involvement of the anterior and posterior hemispheres and corresponding asymmetries in activity (see Kinsbourne, 1988, and Levy et al., 1983, for further discussion of the crucial distinction between specialisation and activation with regard to psychopathology and emotion). Such asymmetries in activity are clearly expected to affect the cognitive and information processing functions of specialised regions of the brain (a topic of considerable interest at present: Heller & Nitschke, 1997; Liotti & Tucker, 1995; Tomarken & Keener, this Issue; also Tucker, 1981). However, the reason why anterior asymmetries in brain activity are associated with affective valence in the ways they are is an unanswered question of continuing importance. Some authors (e.g. Liotti & Tucker, 1995; Robinson, Boston, Starkstein, & Price, 1988) have discussed the possibility that different neurotransmitter systems are associated with the behavioural characteristics of different emotional states. Nonetheless, it appears that our understanding of this aspect of the regulation of affect is rudimentary.

Furthermore, the emphasis on regional differences in activity leads to a research agenda in which we would hope to elucidate the mechanisms underlying such asymmetries in activity. Examples of these could include cortically driven phenomena such as cognitions (e.g. Clore, 1994), subcortically driven phenomena such as interactions with the amygdala (e.g. LeDoux, 1993), biochemical phenomena such as dopamine and norepinephrine pathways (e.g. Liotti & Tucker, 1995; Tucker & Williamson, 1984), externally applied phenomena such as electrical impulses, lesions, or even life stress, and stable personality characteristics such as extraversion (Heller, 1993b; Nitschke et al., in prep.).

In summary, our approach to understanding brain function in affective and anxiety disorders has focused on identifying the components of the emotional phenomena accompanying these disorders. In this regard, we have been guided by the circumplex model of emotion, as well as by psychological theories that have attempted to describe the unique characteristics of various emotional states. We have emphasised the importance of considering subtypes of depression and anxiety and their comorbidity when confronted with conflicting results. Using this strategy, we believe that we can piece together some parts of the puzzle as to which regions of the brain are involved in depression and anxiety.

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