Regional Brain Asymmetries in Major Depression with or without an Anxiety Disorder: A Quantitative Electroencephalographic Study

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Studies of brain activity in affective disorders need to distinguish between effects of depression and anxiety because of the substantial comorbidity of these disorders. Based on a model of asymmetric hemispheric activity in depression and anxiety, it was predicted that anxious and nonanxious depressed patients would differ on electroencephalographic (EEG) measures of parietotemporal activity. Resting EEG (eyes closed and eyes open) was recorded from 44 unmedicated outpatients having a unipolar major depressive disorder (19 with and 25 without an anxiety disorder), and 26 normal controls using 30 scalp electrodes (13 homologous pairs over the two hemispheres and four midline sites). As predicted, depressed patients with an anxiety disorder differed from those without an anxiety disorder in alpha asymmetry. Nonanxious depressed patients showed an alpha asymmetry indicative of less activation over right than left posterior sites, whereas anxious depressed patients showed evidence of greater activation over right than left anterior and posterior sites. The findings are discussed in terms of a model in which specific symptom features of depression and anxiety are related to different patterns of regional brain activity. © *1997 Society of Biological Psychiatry*

Key Words: Depressive disorders, anxiety disorders, electroencephalography, alpha asymmetry, brain laterality

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Introduction

Electroencephalographic (EEG) studies have found greater alpha power over left than right frontal regions during transient induction of depressed mood (Tucker et al 1981), in subclinically depressed students (Schaffer et al 1983; Davidson et al 1987), and in currently or previously depressed patients (Henriques and Davidson 1990, 1991). Given that alpha suppression occurs during cortical activation (Shagass 1972), this asymmetry is indicative of relatively less left frontal activation and greater right frontal activation in depression. Davidson (1992) interpreted the anterior asymmetries of alpha power in depres-

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sion as being related to an approach/withdrawal dimension, in which reduced left frontal activation is thought to be associated with a deficit in approach-related behaviors and right frontal activation with withdrawal-related behaviors.

Some studies measuring EEG alpha asymmetry in depressed students or previously depressed subjects have found the opposite pattern of greater right than left alpha power at parietal sites (Davidson et al 1987; Henriques and Davidson 1990), while other studies have not found this posterior asymmetry in depressed students or in patients having a major depressive disorder (Henriques and Davidson 1991; Schaffer et al 1983). The abnormal parietal alpha asymmetry was thought to be associated with evidence of cognitive deficits indicative of right posterior dysfunction in depression (Flor-Henry 1976; Davidson et al 1987; Tucker et al 1981). Heller et al (1995) have suggested that the failure of some EEG studies to find evidence of reduced right parietal activity in depression may have been due to opposing effects of anxiety on parietotemporal activity.

Anxiety is a common clinical feature of depressive disorders. Anxiety and depression appear, however, to be associated with very different abnormalities of hemispheric asymmetry. Selective impairment of visuospatial performance on neuropsychological tests (Flor-Henry 1976; Miller et al 1995) and left hemifield deficits on visual half-field or dichotic listening tests (Bruder et al 1989, 1992; Liotti et al 1991) have suggested that cognitive abnormalities in depressive disorders are more related to right than left hemisphere dysfunction. In contrast, Tucker (1981) reviewed evidence for *left* hemisphere dysfunction in anxiety. High trait anxiety in college students was associated with poor right visual field (left hemisphere) performance on verbal and spatial tasks. Among the anxiety disorders, patients having an obsessive–compulsive disorder were found to display dichotic listening abnormalities suggestive of left hemisphere dysfunction (Wexler and Goodman 1991). In a direct comparison of visual field asymmetries of patients having either an anxiety disorder or depressive disorder (Liotti et al 1991), patients having a dysthymic disorder showed a left visual field (right hemisphere) deficit, whereas patients having a generalized anxiety disorder tended to have the opposite visual field asymmetry.

Given evidence for an association between performance on cognitive tests and electrophysiologic activity at posterior sites (Davidson et al 1990), the above findings suggest that anxiety and depression may be associated with *opposite* hemispheric activity patterns in the parietotemporal region. Heller et al (1995) hypothesized that panic or anxious arousal is associated with right parietotemporal hyperactivition, whereas depression is associated with a right parietotemporal hypoactivation. Their findings for a chimeric faces task, a free-vision task that measures hemispatial bias for face processing, provided support for this hypothesis. Students with high levels of depression had smaller left hemispatial (right hemisphere) biases than those with low depression, whereas students with high levels of trait anxiety had larger left hemispatial (right hemisphere) biases than those with low anxiety. Heller et al did not, however, obtain EEG measures of hemispheric activity, and they tested only subclinical samples.

The present study compared EEG alpha asymmetries of patients having a major depressive disorder (MDD) and patients having *both* a MDD and an anxiety disorder. The following predictions were tested in this study: 1) Depressed patients will in general show relatively greater alpha power over left than right anterior sites, consistent with EEG evidence of left frontal hypoactivation in depression. This prediction should hold for depressed patients with or without an anxiety disorder. 2) Depressed patients with an anxiety disorder should differ from depressed patients without an anxiety disorder in their alpha asymmetry at posterior sites. Specifically, patients with only a depressive disorder will show greater alpha over right than left hemisphere, consistent with evidence of right posterior hypoactivation in depression. In contrast, depressed patients with an anxiety disorder will not show this pattern, and may show the opposite alpha asymmetry consistent with relatively greater right posterior activation.

Methods

Subjects

EEGs were recorded from 44 depressed outpatients who were attending a university-affiliated Depression Evaluation Service at New York State Psychiatric Institute, and from 26 normal controls recruited from hospital personnel, local colleges, and a pool of normal volunteers. All aspects of the diagnostic assessment of patients were carried out by research psychiatrists as part of ongoing treatment protocols. Patients met DSM-III-R criteria for unipolar major depressive disorder. Nineteen of the depressed patients also met DSM-III-R criteria for one or more of the following anxiety disorders: social phobia ($n = 15$), panic disorder ($n = 3$), general anxiety disorder ($n = 1$) or obsessive–compulsive disorder ($n = 1$). These patients will be referred to as the anxious-depressive subgroup. The remaining 25 patients did not meet criteria for an anxiety disorder and will be referred to as the nonanxious-depressive subgroup. Only 1 patient in each subgroup met DSM-III-R criteria for melancholia. The normal controls were screened using a modified version of the Schedule for Affective Disorders and Schizophrenia–Lifetime ver-

Table 1. Subject Characteristics

	Anxious MDD (n = 19)	Nonanxious MDD (n = 25)	Controls (n = 26)
Gender			
Women	9	13	13
Men	10	12	13
Age (years)			
Mean	36.7	41.3	32.9[a]
SD	11.5	10.7	9.8
Education (years)			
Mean	15.2	15.1[b]	16.9[c]
SD	2.5	2.1	1.8
Handedness (LQ)			
Mean	90.1	62.7	69.9
SD	16.0	56.4	51.2
Beck Depression Inventory			
Mean	22.0	21.0[d]	2.2[c]
SD	8.1	8.2	2.6
Trait Anxiety Scale			
Mean	81.3[e]	75.8[d]	48.9[c]
SD	7.6	9.6	9.0
State Anxiety Scale			
Mean	60.6[e]	55.4[d]	44.0[c]
SD	9.0	11.3	6.0

[a] Normal controls differ significantly from nonanxious MDD, $p < .05$.
[b] $n = 22$.
[c] Normal controls differ significantly from anxious MDD and nonanxious MDD, $p < .05$.
[d] $n = 24$.
[e] $n = 18$.

sion (Spitzer and Endicott 1975) to exclude those with current or past psychopathology. Subjects were also excluded if they had current substance abuse or a history of head trauma or other neurological disorder.

Table 1 gives the characteristics of the anxious-depressive, nonanxious-depressive, and normal control groups. There were about equal numbers of women and men in each group. The anxious-depressives ranged in age from 20 to 58 years, the nonanxious-depressives from 23 to 60 years, and the normal controls from 21 to 57 years. There was a small, but statistically significant, difference in mean age among groups, $F(2,67) = 4.03$, $p = .022$. Newman–Keuls multiple comparison tests indicated that the normal controls were younger than the nonanxious-depressives ($p < .05$). There was also a significant difference among groups in mean education, $F(2,64) = 6.00$, $p < .004$, with normal controls having on the average 2 years more education than either patient group. There was, however, no difference in age or education between the anxious- and nonanxious-depressive groups. Nor was there a significant difference among groups in handedness laterality quotients (LQs) on the Edinburgh Handedness Inventory (Oldfield 1971). A LQ score of 100 equals completely right-handed, and −100 equals completely left-handed. Five nonanxious depressed patients and 5 normal controls were left-handed, whereas the remaining depressed patients and normal controls were right-handed.

Mean ratings on the Beck Depression Inventory (Beck et al 1961) were essentially the same for the anxious- and nonanxious-depressive groups (Table 1), but were significantly lower for normal controls, $F(2,66) = 68.34$, $p < .001$. There were also significant differences among groups in scores on the state [$F(2,65) = 20.15$, $p < .001$] and trait [$F(2,65) = 89.38$, $p < .001$] forms of the State–Trait Anxiety Inventory (Spielberger et al 1983). Multiple comparison tests indicated that normal controls had significantly lower mean anxiety scores than either the anxious- or nonanxious-depressive groups ($p < .05$). Although anxious-depressives had the highest mean anxiety scores, there was no significant difference in these ratings between the patient groups. This is likely to reflect the relative lack of specificity of these self-rating scales for assessing anxiety as opposed to depression (Clark and Watson 1991).

Procedure

Patients were tested after a minimum drug-free period of 10 days, with most patients drug-free for a considerably longer period. Resting EEG was recorded while subjects sat quietly in a sound attenuated booth. EEG was recorded during two 3-min periods (eyes open and eyes closed), with the order of these conditions alternated across subjects in each group. Subjects were instructed to remain still and to inhibit blinks or eye movements during each

recording period. During the eyes open condition, subjects fixated on a central cross.

Electrophysiological Recording

Scalp EEG was recorded from 13 lateral pairs of electrodes (FP1, FP2; F3, F4; F7, F8; FC5, FC6; FT9, FT10; C3, C4; T7, T8; CP5, CP6; TP9, TP10; P3, P4; P7, P8; P9, P10; O1, O2) and from four midline electrodes (Fz; Cz; Pz; Oz) using an electrode cap (Electro Cap International, Inc.) with a nose reference. Standard Beckman Ag/AgCl electrodes at supra- and infra-orbital sites surrounding the right eye were used to monitor eyeblinks and vertical eye movements (bipolar), and electrodes at right and left outer canthi monitored horizontal eye movements (bipolar). All electrode impedances were below 5 kΩ. EEG was recorded through a Grass Neurodata acquisition system at a gain of 10 kΩ (5 kΩ for eye channels), with a bandpass of 0.01–30 Hz.

A PC-based EEG acquisition system (NeuroScan) acquired and digitized the data continuously at 100 samples/sec over each 3-min recording period. This period was chosen based on previous studies, which have shown that total recording periods as brief as 2 or 3 min were adequate to produce reliable estimates of alpha power in normal or depressed adults (Henriques and Davidson 1991) or in schizophrenic patients (Lund et al 1995).

Electrophysiological Analyses

Data were segmented into consecutive 1.28-sec epochs every 0.64 sec (50% overlap). Epochs contaminated by blinks, eye movements, and movement-related artifacts were excluded from analyses using a rejection criterion of $\pm$ 100 μV on any channel. These criteria produced artifact-free data, as verified by direct visual inspection of the raw data. The direct current offset of each epoch was then removed, and the EEG was tapered over the entire 1.28 sec using a Hanning window to suppress spectral side lobes (Bendat and Piersol 1971). The Hanning window deemphasizes data near the beginning and end of each epoch. By overlapping the epochs by 50% the attenuated data are restored in the record. This acts to preserve data and introduces minimal redundancy.

These EEG data were subjected to an off-line power spectrum analysis using a fast Fourier transform. Analyses focused on the alpha band because this is the region where prior studies have found differences in hemispheric asymmetries for depressed subjects (Davidson et al 1987; Henriques and Davidson 1990, 1991; Tucker et al 1981). At each electrode, alpha power was averaged for artifact-free epochs spanning each 3-min recording period for each subject, and subsequently integrated over 7.8–12.5 Hz. Logarithms of alpha power were computed to normalize the data. Power in the delta (1–4 Hz), theta (4–8 Hz), and beta (low beta: 13–18 Hz; high beta: 23–33 Hz) frequency bands was also computed so as to determine whether or not these bands showed group differences in hemispheric asymmetry similar to those for alpha power.

The total number of recording epochs entering into each average did not differ for the patient and normal groups in the eyes open [$F(2,67) = 1.18$, ns] or eyes closed [$F(2,67) = 0.24$, ns] conditions. In the eyes open condition, the mean number of epochs was 218 (SD = 50) for anxious-depressives, 216 (SD = 47) for nonanxious-depressives, and 235 (SD = 48) for normal controls. In the eyes closed condition, the mean number of epochs was 233 (SD = 52) for anxious-depressives, 242 (SD = 42) for nonanxious-depressives, and 238 (SD = 42) for normal controls. In addition to analyses using the nose reference, analyses were performed using waveforms that had been digitally referenced to Cz to allow comparisons with other published findings (e.g., Henriques and Davidson 1991).

Statistical Analyses

Previous studies have indicated the importance of regional (e.g., anterior vs. posterior) differences when comparing alpha asymmetry in depressed and nondepressed subjects (Davidson et al 1985; Henriques and Davidson 1991; Schaffer et al 1983). To examine these regional differences and, at the same time, reduce the amount of data in summary statistical analyses, electrode sites were pooled within anterior (left/right: FC5/6; F3/4; F7/8), central (left/right: C3/4; T7/8; CP5/6), and posterior (left/right: P3/4; P7/8; O1/2) regions. Differences in log alpha power were evaluated using repeated measures analysis of variance (ANOVA), with the variables of Group (anxious-depressive, nonanxious-depressive, normal control), Hemisphere (left, right), Region (anterior, central, posterior), and Condition (eyes open, eyes closed). This ANOVA was followed by separate analyses to evaluate the significance of regional differences in alpha asymmetry for each group. One-way ANOVA and Newman–Keuls multiple comparison tests were used to compare alpha asymmetry among groups at each region. *F* ratios were evaluated using degrees of freedom computed using the Greenhouse–Geisser epsilon correction (Jennings and Wood 1976) where appropriate to counteract heterogeneity of variance–covariance matrices associated with repeated measures. Although log transformation is effective in normalizing the power spectrum, it does not necessarily assure that the corresponding asymmetry scores are also Gaussian. The one-way ANOVA of alpha asymmetry scores for each region was therefore repeated using a nonparametric test, i.e., the Kruskal–Wallis test.

Topographic Maps

Differences in log alpha power over the right and left hemisphere were computed for each of the 13 homologous pairs of electrodes. These asymmetry scores were projected onto corresponding electrode sites on a map of the dura overlying the right hemisphere. The asymmetry scores were linearly interpolated between electrode sites, and coded into a 15-color scale. A topographic map of alpha asymmetries was plotted in this manner for anxious- and nonanxious-depressive groups. In addition, a map showing the *difference* in alpha asymmetries between these groups was also plotted by subtracting the alpha asymmetry scores for the two groups at each of the 13 homologous sites and projecting them onto a map of the right hemisphere in the same manner as described above.

Results

Alpha Power as a Function of Region, Condition, and Hemisphere

Table 2 summarizes the results of an overall ANOVA of alpha power for nose and Cz references. As expected, alpha power was maximum at posterior sites and was reduced in the eyes open as opposed to eyes closed condition. This was confirmed by significant Region and Condition main effects and by a Condition by Region interaction. There was also a Condition by Hemisphere interaction. This reflects the smaller alpha (greater activation) over left than right hemisphere in the eyes closed condition, and the opposite alpha asymmetry in the eyes open condition.

Table 2. Results of Overall ANOVA of Alpha Power for Nose and Cz Reference Sites

		Nose reference		Cz reference	
Source	df	*F*	*p*	*F*	*p*
Region	2,134	370.68	<.001	321.93	<.001
Condition	1, 67	231.80	<.001	243.38	<.001
Condition by Region	2,134	112.40	<.001	139.32	<.001
Condition by Hemisphere	1, 67	28.48	<.001	16.46	<.001
Group by Hemisphere	2, 67	4.35	.017	3.32	.042
Group by Hemisphere by Region	4,134	1.90	.120	3.50	.014

Alpha Asymmetry Differences among Groups

Alpha blocking in the eyes open condition was equally present in the three groups. Given the absence of significant interactions involving both Group and Condition, the data presented below for groups are averaged over condition. Figure 1 shows the mean alpha power at anterior, central, and posterior sites over each hemisphere for the three groups (nose reference). There was no significant difference in overall alpha power among the anxious-

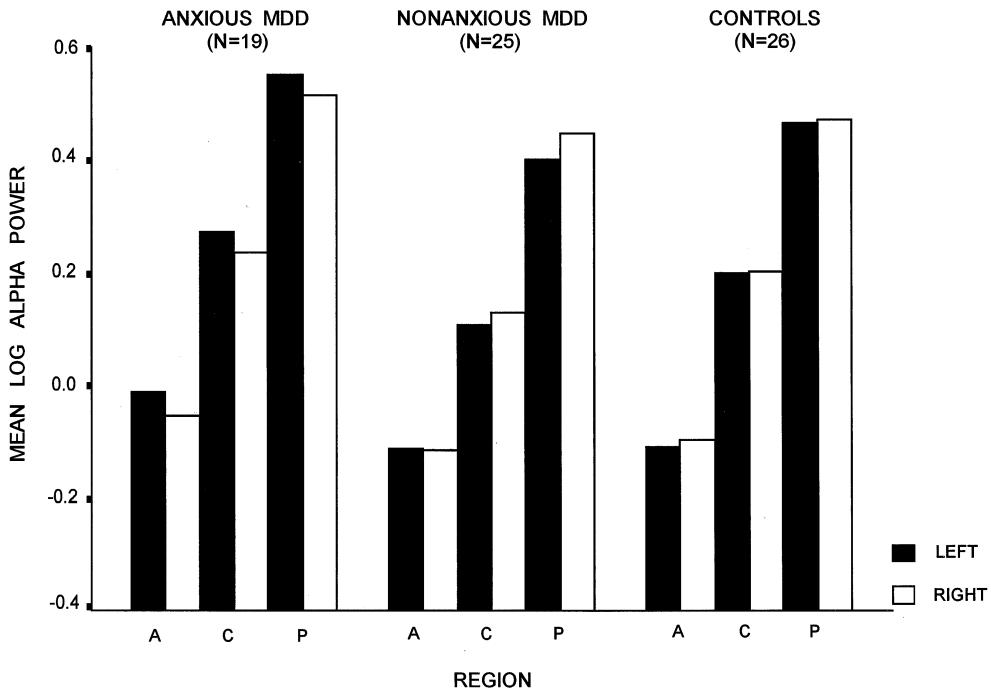

Figure 1. Mean log alpha power (averaged across condition) for anterior (A), central (C), and posterior (P) sites over each hemisphere for the three groups (nose reference).

depressive, nonanxious-depressive, and normal control groups. There were differences among groups in alpha asymmetry, which was shown by a significant Group by Hemisphere interaction in the ANOVA for both nose and Cz reference sites, and by a Group by Hemisphere by Region interaction for the Cz reference (Table 2). Anxious-depressives showed less alpha (greater activation) over the right than left hemisphere sites. An ANOVA of their data indicated that they showed a significant difference in alpha power between hemispheres [$F(1,18) = 5.97$, $p = .025$], and this alpha asymmetry was not dependent on region, i.e., there was no Hemisphere by Region interaction for their data. In contrast, nonanxious-depressives showed greater alpha power (less activation) over the right than left posterior region, but this alpha asymmetry was less evident in the central region and absent in the anterior region. The difference in alpha asymmetry as a function of region in nonanxious-depressives was confirmed by a significant Hemisphere by Region interaction in an ANOVA of their data, $F(2,48) = 4.70$, $p = .02$, $\epsilon = 0.82$. Normal controls differed from both patient groups in failing to show either a significant Hemisphere effect or a Hemisphere by Region interaction in an ANOVA of their data.

To further examine group differences in alpha asymmetry at each region, an alpha asymmetry score was obtained for each subject by computing the difference between the mean log alpha power for the right and left hemisphere regions (Henriques and Davidson 1991). Positive asymmetry scores reflect relatively greater alpha (less activation) over right than left hemisphere sites. A one-way ANOVA of the asymmetry scores for the three groups with a nose reference showed that there were significant differences among groups at anterior sites [$F(2,67) = 3.92$, $p = .025$] and the posterior sites [$F(2,67) = 6.00$, $p = .004$], but not at the central sites. Nonparametric analyses confirmed the existence of significant differences among groups in alpha asymmetry at the anterior sites [$\chi^2(2) = 8.93$, $p = .01$] and the posterior sites [$\chi^2(2) = 9.91$, $p = .007$]. Table 3 gives the mean alpha asymmetry scores for each group at the anterior and posterior sites using a nose reference. The anxious-depressive group showed a negative alpha asymmetry score, indicative of greater activation over right than left anterior sites, whereas nonanxious depressive and normal control groups did not. Multiple comparison tests of the alpha asymmetry scores for the anterior sites with a nose reference indicated that anxious-depressives were significantly different from nonanxious-depressives or normal controls. There was also a significant difference in alpha asymmetry between the anxious-depressive and nonanxious-depressive groups at posterior sites, with nonanxious-depressives showing positive asymmetry scores indicative of less activation over right than left posterior sites, and anxious-depressives showing the opposite direction of posterior asymmetry. The posterior asymmetry for the normal controls was about midway between those for the patient groups, but did not differ significantly from either group.

Table 3. Mean Alpha Asymmetry Scores (Right minus Left Hemisphere) for Groups at Anterior and Posterior Regions for Nose and Cz References

	Anxious MDD	Nonanxious MDD	Controls
Nose reference			
Anterior			
Mean	−.041[a]	−.001	.011
SD	.060	.068	.060
Posterior			
Mean	−.036[b]	.045	.005
SD	.078	.089	.063
Cz reference			
Anterior			
Mean	−.009	−.020	−.019
SD	.051	.061	.056
Posterior			
Mean	−.024[b]	.060	.018[c]
SD	.071	.078	.062

[a] Anxious MDD differ significantly from nonanxious MDD and controls, $p < .05$.
[b] Anxious MDD and nonanxious MDD differ significantly, $p < .05$.
[c] Controls differ significantly from nonanxious MDD, $p < .05$.

Table 3 also gives the mean alpha asymmetry scores for each group using a Cz reference. There was no significant difference in anterior asymmetry among groups with the Cz reference [$F(2,67) = 0.25$, ns]. There was, however, a significant difference among groups in asymmetry scores at posterior sites with the Cz reference [$F(2,67) = 7.74$, $p = .001$]. As was seen for the nose reference, posterior alpha asymmetry was in opposite directions for anxious-depressive and nonanxious-depressive groups. For normal controls, the posterior asymmetry was again midway between those for the patient groups and, with the Cz reference, differed significantly from the asymmetry for the nonanxious-depressive group.

Topographic Maps

The top portion of Figure 2 shows the topography of alpha asymmetries for anxious- and nonanxious-depressives, which are projected onto a lateral view of the right hemisphere. The red–orange regions indicate sites where patients showed relatively greater alpha (less activation) over the right than left side. The blue regions show sites where patients had less alpha (greater activation) over the right than left side. As can be seen, anxious-depressives showed a widespread pattern of relatively greater activation over right than left hemisphere sites at frontal, temporal, and parietal sites. In contrast, nonanxious-

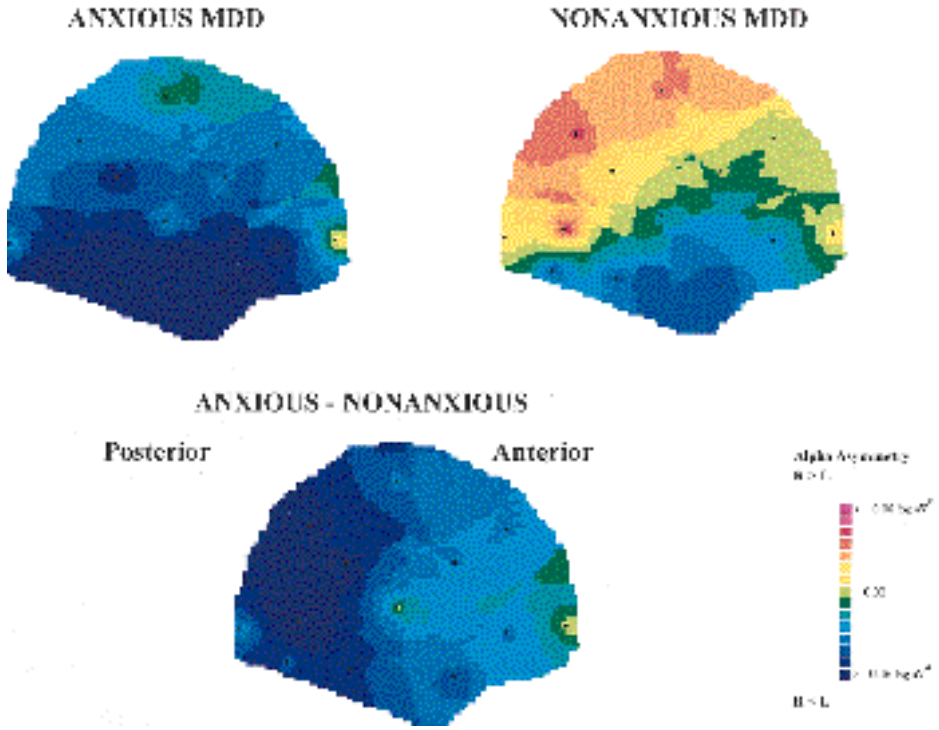

Figure 2. Topographic maps of alpha asymmetry for the anxious-depressive and nonanxious-depressive groups (top). The red-orange regions indicate sites where patients showed greater alpha (less activation) over the right than left side. Blue regions indicate sites where patients had less alpha (greater activation) over the right than left side. The bottom map shows the difference in alpha asymmetry between these groups.

depressives showed less activation over right than left parietotemporal regions. Differences in alpha asymmetries between the anxious- and nonanxious-depressives are also displayed topographically in the lower portion of Figure 2. The dark blue regions highlight the sites in the parietotemporal region where group differences were maximal. At these sites, anxious- and nonanxious-depressives tended to show an opposite direction of alpha asymmetry.

Correlational Analyses

For anterior and posterior regions where there were significant group differences in alpha asymmetry, Pearson correlation coefficients examined the relation between asymmetry scores (right minus left difference in log alpha power) and scores on the Beck Depression Inventory and the State–Trait Anxiety Inventory. No significant correlations were found for patients or normal controls. Correlational analyses also examined the relation of alpha asymmetries and the subject characteristics in Table 1. The only significant correlation was between age of patients and alpha asymmetry at posterior sites ($r = -.29$, $p = .05$ for nose reference and $r = -.34$, $p = .02$ for Cz reference). Older patients tended to have less alpha (greater activation) over right than left posterior sites. This relationship could not account for the opposite direction of posterior asymmetry between anxious- and nonanxious-depressives, because there was no difference in age between these groups. Although nonanxious-depressives were older than normal controls, this difference would have, if anything, reduced the tendency for nonanxious-depressives to show *less* right posterior activation. Also, using age as a covariate in an analysis of covariance (ANCOVA) of the alpha asymmetry scores had no effect on group differences in posterior asymmetry.

Although there was no significant difference among groups in handedness laterality quotients, it was important to rule out possible effects related to the presence of left-handers in the nonanxious-depressive and normal control groups. When analyses comparing alpha asymmetry in the three groups were repeated using only right-handed subjects, the findings were essentially the same as for the total samples.

Other Frequency Bands

Power was also computed for the three other traditional spectral bands. Delta, theta, and beta power were analyzed

using the same repeated measures ANOVA as used for alpha power. In contrast to the above findings for alpha, there was no significant interaction involving the variables of Group and Hemisphere. Thus, the group differences in hemispheric asymmetry appear to be specific to the alpha band.

Discussion

Depressed patients with an anxiety disorder differed significantly from normal controls in their anterior alpha asymmetry using a nose reference, whereas depressed patients without an anxiety disorder did not. The direction of the abnormal alpha asymmetry in anxious-depressives was the same as previously reported for depressed subjects, i.e., relatively greater alpha (less activation) over left than right anterior sites (Davidson et al 1987; Henriques and Davidson 1991; Tucker et al 1981). Studies have also found evidence of increased right anterior cortical activation during anxiety (Davidson et al in submission). Comorbidity of depressive and anxiety disorders may therefore act to heighten the abnormal direction of anterior alpha asymmetry that has generally been seen for depression and anxiety.

As predicted on the basis of the model proposed by Heller et al (1995), depressed patients with an anxiety disorder had the *opposite* direction of alpha asymmetry in the posterior region when compared to depressed patients without an anxiety disorder. This was found for both nose and Cz reference sites. Nonanxious-depressed patients showed evidence of less activation at right than left posterior sites, which agrees with prior reports of right parietal hypoactivation in subclinically depressed subjects (Davidson et al 1987) and previously depressed patients (Henriques and Davidson 1991). This is also consistent with reports of visuospatial deficits and reduced left hemifield (right hemisphere) advantages for nonverbal stimuli in depressed patients (Flor-Henry 1976; Jaeger et al 1987; Liotti et al 1991; Bruder et al 1989, 1992; Miller et al 1995). It supports the hypothesis that major depression, in the absence of significant anxiety symptoms, is associated with right parietotemporal hypoactivation. In contrast, depressed patients with an anxiety disorder showed evidence of greater activation over right than left posterior sites. The abnormal alpha asymmetry in anxious-depressives may be related to hyperactivation of right parietotemporal regions due to anxious arousal (Heller et al 1995), to left hemisphere hypofunction as evidenced by prior behavioral laterality findings for anxiety disorders or anxious subjects (Liotti et al 1991; Tucker 1981; Wexler and Goodman 1991), or to some combination of both.

Theoretical Implications

In attempting to understand the different alterations of hemispheric asymmetry associated with depression and anxiety, it may be helpful to relate these alterations to specific symptom features of these disorders. Clark and Watson (1991) proposed a tripartite model, in which symptoms of depression and anxiety are grouped into three subtypes. The first subtype includes symptoms of general distress and negative affect that are common to both depression and anxiety. There is now considerable evidence that affective behavior is related to frontal activational asymmetries, with negative affect or withdrawal behaviors being associated with right frontal activation, and positive affect or approach behaviors being associated with left frontal activation (for reviews see Davidson and Tomarken 1989; Davidson 1992). The presence of *both* a decrease in left frontal activation associated with a deficit in approach behavior or positive affect in depressive disorders and an increase in right frontal activation associated with withdrawal behaviors in anxiety disorders such as social phobia or panic might therefore account for the heightened abnormality of anterior alpha asymmetry for comorbidity of these disorders. The second subtype in Clark and Watson's model includes symptoms of somatic hyperarousal and tension that are specific to anxiety. Heller et al (1995) reviewed evidence suggesting that somatic manifestations of anxious arousal, as for instance seen in panic disorders, are associated with activation of the right parietal region. Our finding of less alpha (greater activation) over right than left posterior sites in depressed patients with anxiety disorders, but not in nonanxious depressed patients, supports this association of anxious arousal with right parietal hyperactivation. The third subtype includes symptoms of anhedonia and absence of positive affect, which are specific to depression. Patients having a MDD with melancholia, which involves the cardinal symptom of anhedonia, were particularly likely to show a pattern of dichotic listening suggestive of right hemisphere dysfunction (Bruder et al 1989). Also, among depressed patients with predominantly nonmelancholic disorders, those with high scores on a physical anhedonia scale (Chapman and Chapman 1978) failed to show greater amplitude of the P3 brain potential over right than left central sites to complex tone stimuli (Bruder et al 1996). These findings suggest that depression with physical anhedonia may involve hypoactivation of right temporoparietal regions. In the present study, nonanxious depressed patients did show alpha asymmetries indicative of less right than left posterior activation. In summary, the three symptom subtypes of depression and anxiety in Clark and Watson's model—negative affect, somatic hy-

perarousal, and anhedonia—appear to involve specific patterns of regional hemispheric activity.

Clinical Implications

There is considerable comorbidity of depressive and anxiety disorders (Maser and Cloninger 1990). For instance, 43% of the depressed outpatients in the present study also had an anxiety disorder. Moreover, self-rating scales for depression and anxiety are highly correlated. The correlation between ratings of patients on the Beck Depression Inventory and on the trait version of the State–Trait Anxiety Inventory was .61 in the present study. The lack of specificity of the State–Trait Anxiety Inventory for assessing anxiety, as opposed to depression, may explain why the anxious- and nonanxious-depressive groups were not significantly different on this self-rating scale. Considerable effort has recently been directed at developing measures that could distinguish between depression and anxiety, with some success in the psychometric domain (e.g., see Watson et al 1995). The findings of the present study suggest that measures of alpha asymmetry at parietotemporal sites might be of some value in distinguishing anxious- and nonanxious-depressive disorders. Further research is, however, needed to determine how these differences in alpha asymmetry relate to scales for differentiating anxious arousal and depression (Watson and Clark 1991) and to autonomic measures of anxious arousal, e.g., skin conductance or heart rate measures.

Methodological Implications

The opposite direction of posterior alpha asymmetry in depressed patients with an anxiety disorder as compared to those without an anxiety disorder underscores the importance of taking this type of comorbidity into account in electrophysiological and neuropsychological studies of depression. Opposing hemispheric activity patterns in anxiety and depression may explain why some EEG studies did not find a reduction of right parietal activity in depression, as suggested by Heller et al (1995) and supported by the present study. A similar argument can also be made concerning findings of studies using neuropsychological or perceptual asymmetry tests that are sensitive to activational asymmetries in temporoparietal regions (Davidson and Tomarken 1989). Future studies should incorporate in their design a way of separating out the effects of depression and anxiety on hemispheric activation. In this regard, the present study was limited by the lack of a group of patients having an anxiety disorder with little or no depression. Also, depressed patients without an anxiety disorder will still have some anxiety symptoms. Rating scales or direct electrophysiologic measures of anxious arousal could be of value in future studies in selecting depressed patients with low versus high anxiety levels. Finally, the anxiety disorder present in most of the anxious-depressive patients was social phobia. Although there is reason to believe that patients with other anxiety disorders, e.g., generalized anxiety disorder or panic disorder, show activational asymmetries similar to those observed for the anxious-depressive patients (Liotti et al 1991; Heller et al 1995), additional study is needed to establish the generalizability of these findings.

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