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Regional Brain Electrical Asymmetries Discriminate Between Previously Depressed and Healthy Control Subjects

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Baseline resting electroencephalogram (EEG) activity was recorded from 6 normothymic depressives and 8 controls using three different reference montages. Power in all frequency bands was extracted by Fourier transformation. Significant Group × Region × Hemisphere interactions were found consistently for alpha band power only. Previously depressed subjects had less left-sided anterior and less right-sided posterior activation (i.e., more alpha activity) than did never depressed subjects. Previously depressed subjects had no history of pharmacological treatment and did not differ from controls in emotional state at the time of testing. The pattern of anterior and posterior asymmetry in the previously depressed subjects is similar to that found in acutely depressed subjects and suggests that this may be a state-independent marker for depression.

Research that has focused on regional cerebral activation suggests that depression is associated with an alteration in the normal pattern of hemispheric functioning (Davidson, 1988a). The initial impetus for studying hemispheric dysfunction in depression came from early studies on affective disturbance in brain-damaged patients (e.g., Gainotti, 1972). A number of investigators consistently observed symptoms of depression and anxiety in patients with left hemisphere lesions (see Davidson, 1984; Tucker, 1981, for reviews). More recently, Robinson and his colleagues, using computerized tomography (CT), have specified with increased precision the relation between stroke location and poststroke mood changes (Robinson, Kubos, Starr, Rao, & Price, 1984; Robinson & Price, 1982). Of particular relevance was the finding that the severity of poststroke depression was positively correlated with the lesion's proximity to the left frontal pole and negatively correlated with proximity to the right frontal pole (Robinson et al., 1984). It is important to note that the depression that occurs subsequent to left anterior stroke is phenomenologically indistinguishable from unipolar major depression (Lipsey, Spencer, Rabins, & Robinson, 1986). If we assume that stroke-produced lesions lead to decreased activation in the brain regions in which they are found (Burke et al., 1982; Takeuchi et al., 1986), these findings suggest that depression is associated with a decrease in either left frontal or right posterior activation.

Studies that have looked for asymmetrical activation using either regional cerebral blood flow (rCBF) or cerebral glucose metabolism have produced inconsistent results (see Henriques & Davidson, 1989, for review). Some researchers have found decreased left anterior activation as reflected by decreases in glucose metabolism in those regions (Baxter et al., 1985; Baxter et al., 1989; Kuhl, Metter, & Riege, 1985), whereas others have not (Gur et al., 1984). Uytdenhoef et al. (1983) did not find that depressed subjects had diminished left anterior activation, but did find that these subjects had decreased cerebral blood flow in the right posterior region as compared with control subjects, suggestive of decreased activation in that area. It is conceivable that the inconsistencies in these studies reflect different subgroups of depressives.

Previous work in our laboratory has used quantitative electroencephalography (EEG) to examine patterns of regional cerebral activation in depression. This work has found that depressed subjects differed from nondepressed subjects in measures of alpha asymmetry in the anterior and posterior scalp regions (Davidson, Schaffer, & Saron, 1985; Schaffer, Davidson, & Saron, 1983). Compared with control subjects, depressed subjects had increased left frontal alpha power and a pattern of more right-sided alpha power in the parietal region. Because a large body of literature indicates that decreases in alpha band activity are associated with increases in cortical activation (see Davidson, 1988b; Lindsley & Wicke, 1974), we interpreted these results as indicating that depressed subjects have decreased left frontal activation and decreased right parietal activation as compared with control subjects. We recently replicated these earlier results using a larger number of subjects (Davidson, Chapman, & Chapman, 1987).

Relatively few studies have investigated state-independent differences in central activation between depressed and nondepressed subjects. Ulrich and colleagues (Ulrich, Renfordt, Zeller, & Frick, 1984) recorded EEG activation only over the occipital region during drug treatment. These investigators found that depressives who responded to drug treatment showed decreases in both left and right occipital activation on recovery.

It may be that the asymmetries we have observed are state independent, and if so, EEG asymmetries may be useful in the identification of subjects at risk for depression. Before embarking on a longitudinal study, one must demonstrate that these patterns of cerebral asymmetry are present in a group of subjects already identified as being at risk for depression. Recent

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work by Lewinsohn, Hoberman, and Rosenbaum (1988) investigating various risk factors for unipolar depression found that interviewer-rated past depression was the best predictor of future depression. Similar results were obtained in a study that examined risk factors for postpartum depression (O'Hara, Neunaber, & Zekoski, 1984). These findings suggest that subjects who have experienced a previous depressive episode are at increased risk for a future depression. Thus, it would be informative to examine regional EEG asymmetries in remitted depressives as a first step in establishing the validity of such measures as predictors of vulnerability to depressive disorders.

In this study, we tested a group of normothymic subjects who were diagnosed as having a previous episode of depression and compared them with a matched group of control subjects who had no history of depression or any other psychopathology in either themselves or their first-degree relatives. We recorded EEG from the left and right hemisphere in several anterior and posterior brain regions. Our previous studies of regional brain asymmetries in depressed and nondepressed subjects were restricted to the analysis of power in the alpha band. In this study, in addition to assessing power in the alpha band, we examined power in the other EEG frequency bands to ascertain whether the predicted group differences were specific to the alpha band. Another methodological improvement made in this study was the use of multiple reference montages. Considerable discussion has appeared in the electrophysiology literature concerning the appropriateness of different referencing strategies (Lehman, 1987; Nunez, 1981). Whereas some investigators have argued for particular approaches over others, there is currently no consensus in the literature regarding which approach is optimal. Therefore, in the present study, we chose to record our data in a fashion that would permit the derivation of EEG using three different references: (a) vertex, (b) computer-averaged ear lobes, and (c) average reference. The computer-averaged ear lobe reference is one we have developed to avoid the problem, noted by Nunez (1981), that is involved in physically linking the two ear lobes (Davidson, 1988b). Nunez observed that the physical linking of the two ears attenuated the magnitude of observed asymmetry by providing a low-resistive shunt across the head that forced the two sides to be isoelectric. Our computer-averaged ear reference is obtained by recording separate channels of Cz-A1 (vertex referenced to left ear) and Cz-A2 (vertex referenced to right ear) and then computer averaging these channels. In addition to computing measures of power in the traditional EEG bands, we computed power in a high frequency (65–75 Hz) band (which presumably is purely myogenic in origin) to obtain estimates of muscle contamination. Power in this band was then used as a covariate in our analyses of EEG band power. Subjects' self-reports of emotion were obtained following each baseline trial to ensure that differences in EEG activation were not the result of differences in emotional state at the time of testing.

We predicted that the pattern of EEG asymmetry across the scalp would distinguish between previously depressed and never-depressed subjects and that this would be consistent across reference montage. On the basis of our earlier work (Davidson et al., 1987; Schaffer et al., 1983), we predicted that previously depressed subjects, as compared with never-depressed subjects, would have less left frontal activation and less right parietal activation as reflected by more alpha power in those regions.

Table 1
Subject Characteristics

	Group			
	Never depressed		Previously depressed	
Characteristic	*M*	*SD*	*M*	*SD*
Age (years)	37.37	9.52	34.67	3.44
SES	2.50	0.93	2.83	0.98
HDRS	1.75	1.49	1.16	1.60
BDI	1.43	2.15	1.67	2.25
Ratio women/men	6/2		5/1	

Note. Socioeconomic status (SES) is rated 1–7; lower numbers reflect higher social class. HDRS = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory.

Method

Subjects

Subjects were recruited through the local newspapers via advertisements requesting subjects for participation in a study of emotion. All subjects were screened with the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978). Interviews were conducted by one of two laboratory members, both of whom had completed 40 hours of SADS training. Out of 46 possible subjects interviewed, 20 met all criteria and were invited to participate in the study. The 9 subjects (1 man and 8 women) in the previously depressed group included 3 subjects with past major depression and 6 who met criteria for past minor depression according to Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978). All previously depressed subjects had been free of depressive symptoms for at least 1 year. None of the previously depressed subjects had received medication for the treatment of their depressions. The never-depressed group consisted of 11 subjects (4 men and 7 women). All of the never-depressed subjects were required to have an absence of psychiatric illness in their first-degree relatives, and all subjects were right-handed as assessed by the Edinburgh Inventory (Oldfield, 1971).

Because of equipment malfunctions, data from 1 subject in each group were lost. Another 2 subjects in each group had excessive artifact during one of the two baseline trials and thus were dropped prior to analysis. This resulted in a final group of 6 previously depressed (1 major depression, 5 minor depression) and 8 never-depressed subjects. The two groups did not differ in age, $t(9.3) = 0.74$, $p > .05$, sex, $p > .05$, Fisher's Exact (2-tail), or SES, as assessed by the Hollingshead Inventory, (Hollingshead, 1957), $t(12) = -0.65$, $p > .05$. There were no group differences in the amount of reported depression as assessed by the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, & Erbaugh, 1961), $t(11) = -0.19$, $p > .05$, or the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), $t(12) = 0.70$, $p > .05$. Relevant subject variables are listed in Table 1.

Procedure

Prior to the EEG recording, the subject was informed as to the nature of the experiment and was asked to sign a consent form. The subject was then administered the HDRS and completed the BDI. On completion of the depression inventories, the subject was escorted to the experimental testing room where all further procedures took place.

The test session consisted of two 30-s baseline resting periods, and these baselines were followed by a series of emotion-eliciting film clips.

This report will present only the data from the baseline periods. Baseline EEG was recorded during both an eyes-open and an eyes-closed rest period. The subjects were asked, at the end of each baseline trial, to rate their emotional state during the trial. This was done by rating emotional experience on seven emotion scales: interest, amusement, happiness, fear, sadness, disgust, and anger. Subjects used a 0–8 scale, with 0 indicating that the emotion was not experienced during the trial and 8 indicating that it was felt very strongly during the trial. The purpose of obtaining ratings of emotional state during the baseline trials was to examine possible group differences in self-reported mood at the time of electrophysiological recording. This information was critical to our evaluation of our hypothesis that the measures of brain electrical asymmetry are state-independent markers of vulnerability to depression.

All subject instructions were presented on a video monitor (Sony 27-in. [61-cm] XBR); their presentation was controlled by computer. The subjects used a numeric keypad to advance through the instructions and to input their emotion ratings at the end of each trial. Subjects were instructed to use either their right or their left hand to enter their responses, and response hand was randomized across subjects.

EEG Recording

EEG was recorded with a modified lycra electrode cap (Electro-cap). The electrode cap is positioned on the subject's head using known anatomical landmarks. Elastic straps from the cap attach to a strap that traverses the subject's torso, and this enables the subject to move comfortably without altering the electrode placement. This procedure results in accurate electrode placements (Bloom & Anneveldt, 1982). EEG was recorded from 14 scalp locations: F3, F4, F7, F8, T3, T4, T5, T6, P3, P4, C3, C4, Pz, and Fz (10–20 system). All placements were referenced to Cz. Two additional channels were recorded in order to derive an averaged ears reference: Cz-A1 and Cz-A2. Electrode impedances were all under 5,000 ohms, and the impedances for homologous sites were within 500 ohms of each other. EOG was recorded from the external canthus to the supra-orbit of one eye, in order to facilitate artifact scoring.[1]

EEG and electrooculogram (EOG) were amplified with a 20-channel Grass Model 12 Neurodata System that had a bandpass of 1–300 Hz and a 60-Hz notch filter. All analog signals were passed through active, low-pass filters (Rockland model 424) with a cut-off of 85 Hz and a 24-dB/octave roll-off (see Dumermuth & Molinari, 1987). The EEG was digitized at the rate of 250 samples/s. The EEG activity for eight channels and the EOG activity were displayed on a Grass Model 7, 9-channel polygraph. This paper record was then used to identify those portions of data to be edited out because of eye blinks, gross muscle artifact, and movement artifact.

A Fast Fourier Transform (FFT) was applied to all chunks of artifact-free data that were 2.05 s in duration, with chunks overlapping by 75%. The two groups did not differ in the number of artifact-free chunks, $t(12) = -1.57$, $p > .05$). The mean number of chunks for the never-depressed group was 70.88 (SD = 25.30); the mean for the previously depressed group was 88.67 (SD = 12.63). Averages across all chunks within each baseline trial were then computed. The FFT output was then converted to power density (μV^2/Hz) in each of five bands: delta (1–4 hz), theta (4–8 Hz), alpha (8–13 Hz), beta 1 (13–20 Hz), and electromyogram (EMG; 65–75 Hz), by summing activity across all bins within a band and dividing by the number of 1-Hz bins. Power in the 65–75-Hz band was examined in an attempt to evaluate the presence and amount of muscle artifact quantitatively. Activity in this frequency range is presumed to be exclusively myogenic in origin and thus can be used to estimate the contribution of muscle artifact in each lead independent of EEG activity. In addition to the original recording montage (referencing to vertex), the EEG was recomputed off-line for two additional references: computer-averaged ears and an average reference. For the ears reference, the separate Cz−A1 and Cz−A2 channels were averaged and then added to the original vertex-referenced data.[2] For the average reference, the voltage at each electrode was expressed as a difference from the average voltage of all electrodes on the scalp. All power density values were log-transformed to normalize their distribution.

Table 2
Mean Self-Reported Emotion Averaged Across Eyes-Open and Eyes-Closed Resting Baselines

	Group			
	Never depressed		Previously depressed	
Emotion	*M*	*SD*	*M*	*SD*
Interest	2.00	2.12	2.92	1.36
Amusement	0.75	1.07	1.42	1.50
Happiness	1.25	1.39	2.42	2.04
Sadness	0.50	1.41	0.25	0.61
Fear	0.06	0.17	0.08	0.20
Disgust	0	0	0.25	0.61
Anger	0	0	0.25	0.61

Note. Each emotion was rated on a 0–8 scale.

Results

The emotion self-report data will be presented first, followed by the EEG data. The Huynh-Feldt correction was used in the computation of p values, and an alpha level of .05 was set as criterion for experimental results.

Baseline Emotion Data

Subjects' self-report of experienced emotion was examined by computing separate two-way analyses of variance (ANOVAs), with group and condition (eyes-open/eyes-closed) as variables, for each of the seven emotions that subjects were asked to rate. There were no significant main effects or interactions for any of the rated emotions (Table 2).

Baseline EEG Data

Because previous studies in our laboratory have primarily used alpha power as a dependent measure, we had specific

[1] EOG was only recorded on paper for the purpose of artifact scoring. We thus were unable to digitize EOG activity.

[2] We recorded the Cz channel referenced separately to each ear, rather than reference each ear to Cz, and thus the average of the Cz-A1 and Cz-A2 channels was added to the original data to derive the computer averaged ears reference. To derive this reference, the following equations are used (the derivation for site F3 is used as an example):

$$F3 - Cz + (Cz - A1 + Cz - A2)/2 \quad (1)$$

$$F3 - Cz + Cz - (A1 + A2)/2 \quad (2)$$

$$F3 - (A1 + A2)/2 \quad (3)$$

In these equations, we are assuming that the output of a channel with two inputs (e.g., Cz − A1) is equivalent to the potential difference between these sites. This assumption is warranted in light of the fact that the common mode rejection of the Grass Model 12 amplifiers is 10,000: 1. Thus, in the equations, we use a minus sign rather than a hyphen between each electrode combination.

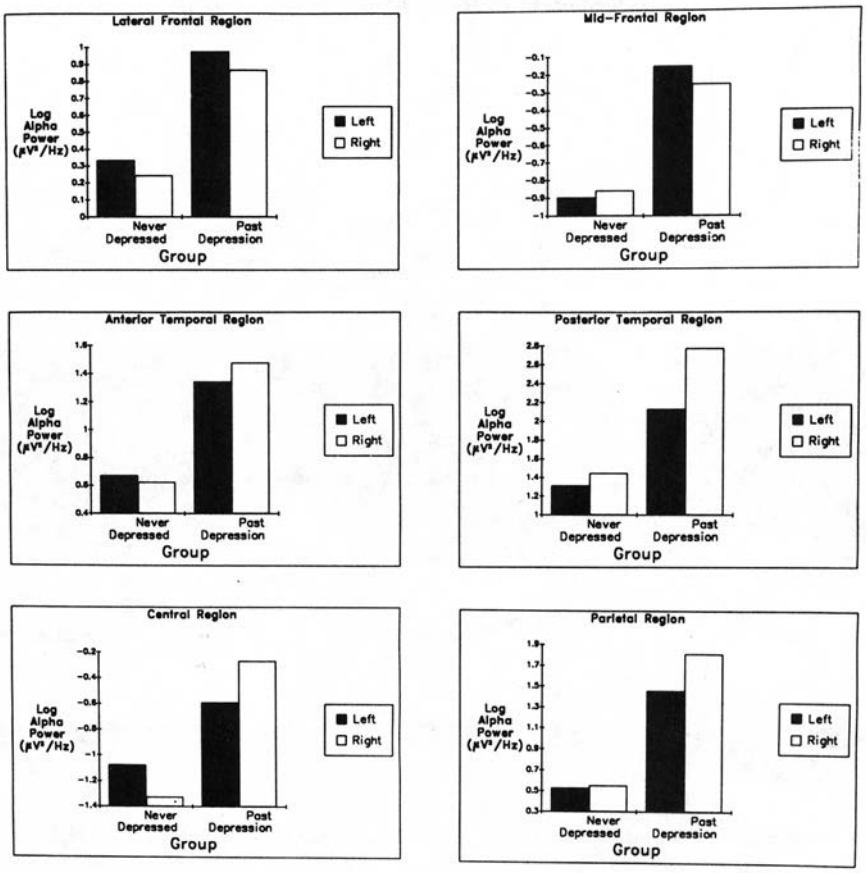

Figure 1. Mean log-transformed alpha (8–13 Hz) power (in $\mu V^2/Hz$) for Cz-referenced EEG (averaged across eyes-open and eyes-closed baselines), split by group and hemisphere, for each region separately. (Decreases in alpha power indicate increased activation.)

hypotheses about activity in this frequency band. Power in the alpha band was therefore examined first, and the structure of the analyses of power in the other frequency bands was based on the observed effects in the alpha band. Four-way ANOVAs were computed with group (previously depressed/never depressed) as the between-groups variable. Within-group variables were hemisphere (left/right), region (midfrontal [F3/4]/lateral frontal [F7/8]/anterior temporal [T3/4]/posterior temporal [T5/6]/central [C3/4]/parietal [P3/4]), and condition (eyes-open/eyes-closed).

Alpha

Cz montage. The analysis of alpha power from Cz-referenced data revealed a significant Group × Region × Hemisphere interaction, $F(5, 60) = 3.34$, $p \leq .05$. Previously depressed subjects had relatively more left frontal alpha activity and relatively more right-sided alpha in the posterior temporal, central, and parietal regions than did never-depressed control subjects (Figure 1). Because there were no interactions between baseline condition and group, a composite variable was created that was the average of the eyes-open and eyes-closed data. This composite variable was then used to decompose the obtained three-way interaction in separate two-way ANOVAs (Group × Hemisphere) computed for each region. These analyses revealed significant Group × Hemisphere interactions in both the posterior temporal, $F(1, 12) = 4.99$, $p \leq .05$, and central, $F(1, 12) = 9.57$, $p \leq .05$, regions. These effects resulted because previously depressed subjects displayed more right-sided alpha (i.e., less activation) in both of these regions, than did the never-depressed subjects.

In order to better visualize the differences in the pattern of asymmetrical activation between the two groups, a topographic difference map was created that displays the differences in alpha-power density between the two groups (Figure 2-1). At each site, the mean log alpha power of the previously depressed subjects was subtracted from the mean log alpha power of the never-depressed subjects. Lighter shading reflects areas where the never-depressed subjects had more absolute activation (i.e., less alpha power) than did previously depressed subjects. Examining the right/left differences, the never-depressed subjects had more left midfrontal and more right posterior activation than did the previously depressed subjects.

Averaged ears montage. The Group × Region × Hemisphere interaction for this reference montage was marginally significant, $F(5, 60) = 2.78$, $p \leq .07$. The pattern of group differences was the same as observed in the Cz-referenced data: previously depressed subjects displayed more left frontal and more right posterior alpha activity than did control subjects (Figure 3).

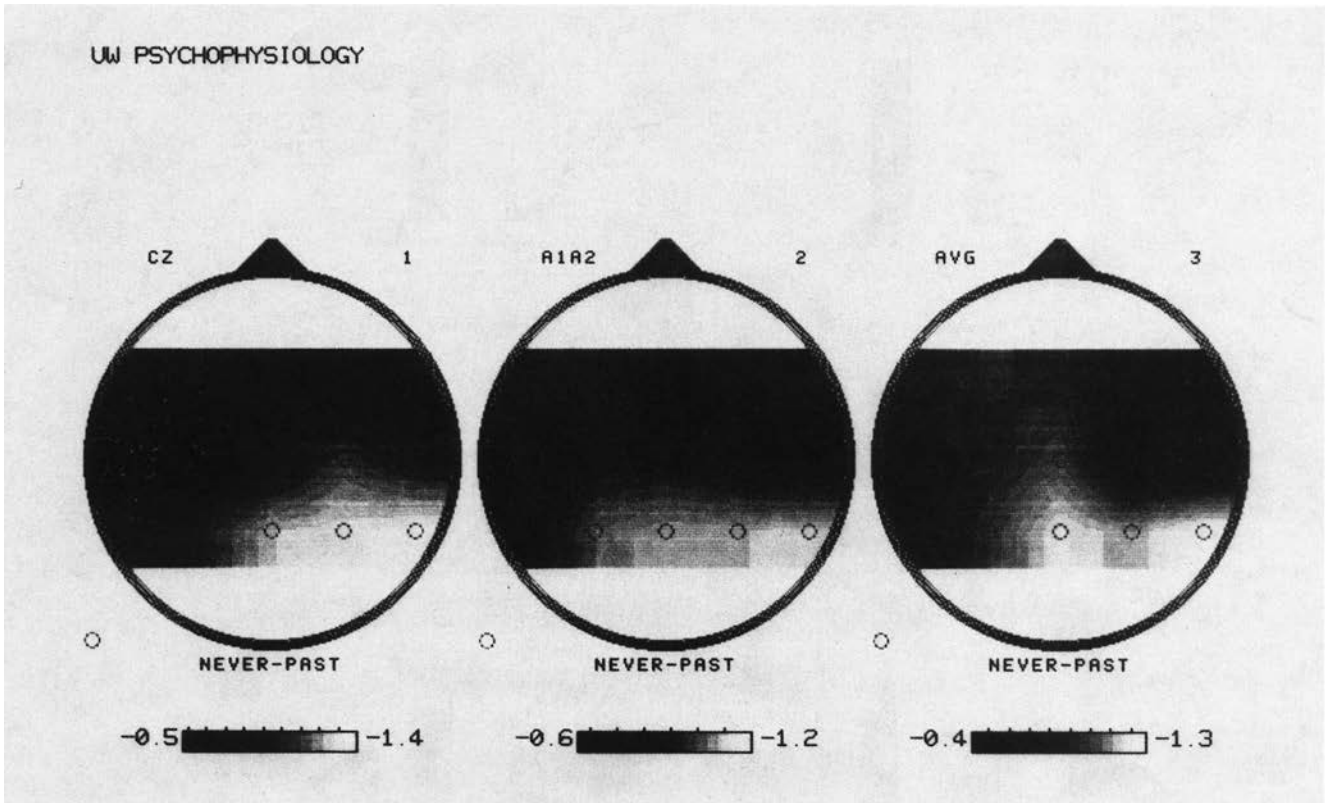

Figure 2. Topographic maps displaying the difference in mean log-transformed alpha (8–13 Hz) power (in $\mu V^2/Hz$) between never-depressed and previously depressed subjects, (1) referenced to Cz, (2) referenced to averaged ears, and (3) referenced to an average reference. (Lighter colors reflect areas where never-depressed subjects have more absolute activation [i.e., less alpha power] than do previously depressed subjects. The frontal pole and occipital regions are blank because no electrodes were placed in these locations.)

Two-way ANOVAs with group and hemisphere as variables (across the two baseline conditions) were computed for each region to decompose the three-way interaction. These analyses revealed a significant Group × Hemisphere interaction in the midfrontal region, $F(1, 12) = 13.79$ $p \leq .05$, and a marginally significant Group × Hemisphere interaction in the lateral frontal region, $F(1, 12) = 4.41$, $p \leq .06$ (Figure 3). The direction of these effects was that previously depressed subjects had more left-sided anterior alpha than did the never-depressed subjects. Figure 2-2 illustrates the group differences in the patterning of regional alpha power. This map shows once again that previously depressed subjects had less left frontal and less right posterior activation (i.e., more alpha) than did the never-depressed control subjects.

Average reference montage. Analysis of alpha power referenced to an average reference again revealed a significant Group × Region × Hemisphere interaction, $F(5, 60) = 3.08$, $p \leq .05$. The data revealed the same pattern of activation as seen in the Cz and averaged-ears montage: Previously depressed subjects had more left-sided alpha power in the anterior regions and more right-sided alpha in the posterior regions than did never depressed subjects (Figure 4). When separate Group × Hemisphere ANOVAs were computed across the two baseline conditions, none of the Group × Hemisphere interactions achieved significance. The topographic map of the group differences in average referenced alpha power is displayed in Figure 2-3. This map is similar to the difference maps of the Cz-referenced and averaged-ears-referenced data in showing that previously depressed subjects have decreased left anterior activation and decreased right posterior activation in comparison with never-depressed control subjects.

The analyses of alpha power showed a consistent pattern of group differences, irrespective of which reference montage was used. Subjects who had a past depressive episode had decreased activation in the left anterior and right posterior regions compared with subjects who had never been depressed, as reflected by more alpha power in these regions.

Other Frequency Bands

The analyses of the other frequency bands was guided by the results of the alpha analyses.

Delta

Cz montage. The analyses of power in the delta band referenced to Cz revealed no significant main effects for group or interactions with group.

Averaged ears montage. This analysis revealed a significant Group × Region × Hemisphere interaction, $F(5, 60) = 3.59$,

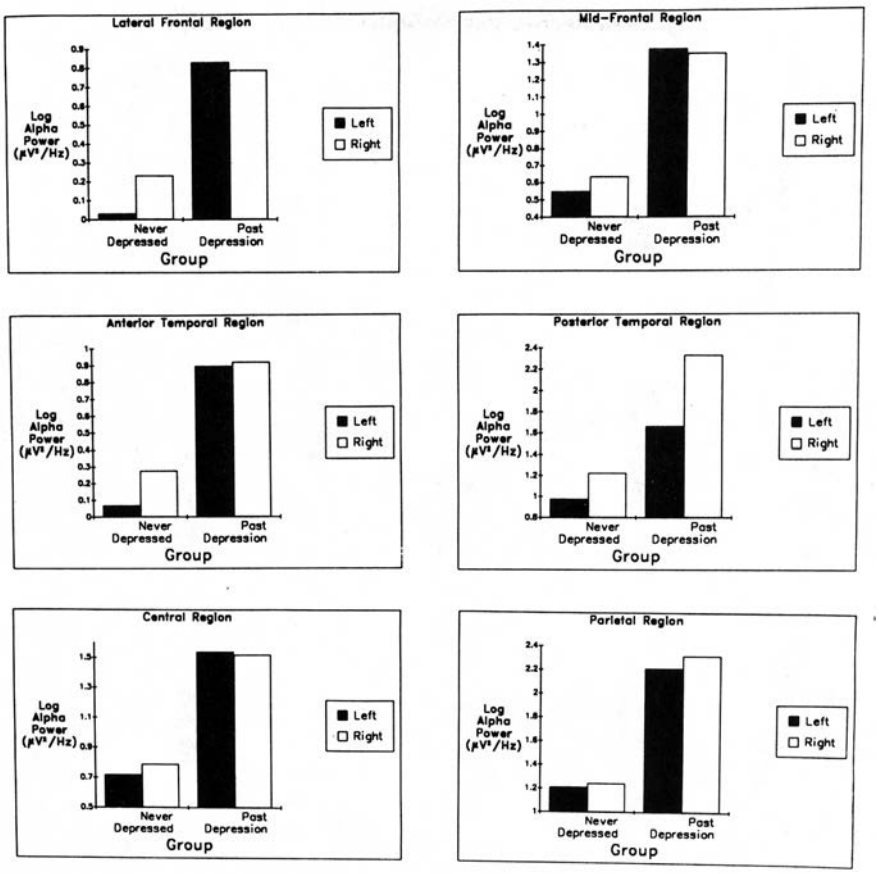

Figure 3. Mean log-transformed alpha (8–13 Hz) power (in μV^2/Hz) for averaged ears-referenced EEG (across eyes-open and eyes-closed baselines), split by group and hemisphere, for each region separately.

$p \leq .05$. Separate Group × Hemisphere ANOVAs were computed for each region to localize the source of this interaction. The lateral frontal region was the only region where this interaction was significant, $F(1, 12) = 5.96$, $p \leq .05$. This was a result of previously depressed subjects' having more left than right delta power in the lateral frontal region, whereas control subjects who had no past depression had more right than left delta power (Table 3).

Average reference montage. Analysis of delta power for this reference revealed no significant main effects for group or interactions with group.

Theta

No significant main effects for group or interactions with group emerged in the analysis of theta band power for any of the three reference montages.

Beta

The analysis of power in the beta frequency band revealed no significant main effects for group or interactions with group for any of the three reference montages.

EMG

Never-depressed and previously depressed subjects did not differ in the amount or patterning of EMG band power (65–75 Hz). Most subjects had little or no activity in this frequency band. When EMG band power was examined for the Cz reference, there were 7 subjects (4 previously depressed) who had any EMG activity. In all but one case, the EMG activity was confined to the anterior temporal region, and no subject had EMG activity in more than two regions. Analysis of EMG activity for the averaged ears reference revealed 11 subjects (6 previously depressed) who exhibited any activity in this frequency band. Three subjects (1 previously depressed) had EMG activity in all brain regions, 6 had activity only in the temporal regions, one had activity in the central and anterior temporal regions, and the last had activity only in the lateral frontal region. Seven of the subjects (4 previously depressed) had activity in this band when the average reference was used. All but one of these subjects had EMG activity confined to the anterior temporal region.

To investigate the possibility that the effects we observed in the alpha band were merely the result of underlying EMG asymmetries, we recomputed our significant regional asymmetry effects in alpha band power using EMG asymmetry (log right [R] − log left [L] EMG power) at that site as a covariate in a series of one-way analyses of covariance (ANCOVAs). These ANCOVAs were computed separately for each region, with group as the independent variable. An asymmetry metric was used rather than the raw power values so that there was only a single covariate for each analysis, rather than multiple covariates. The

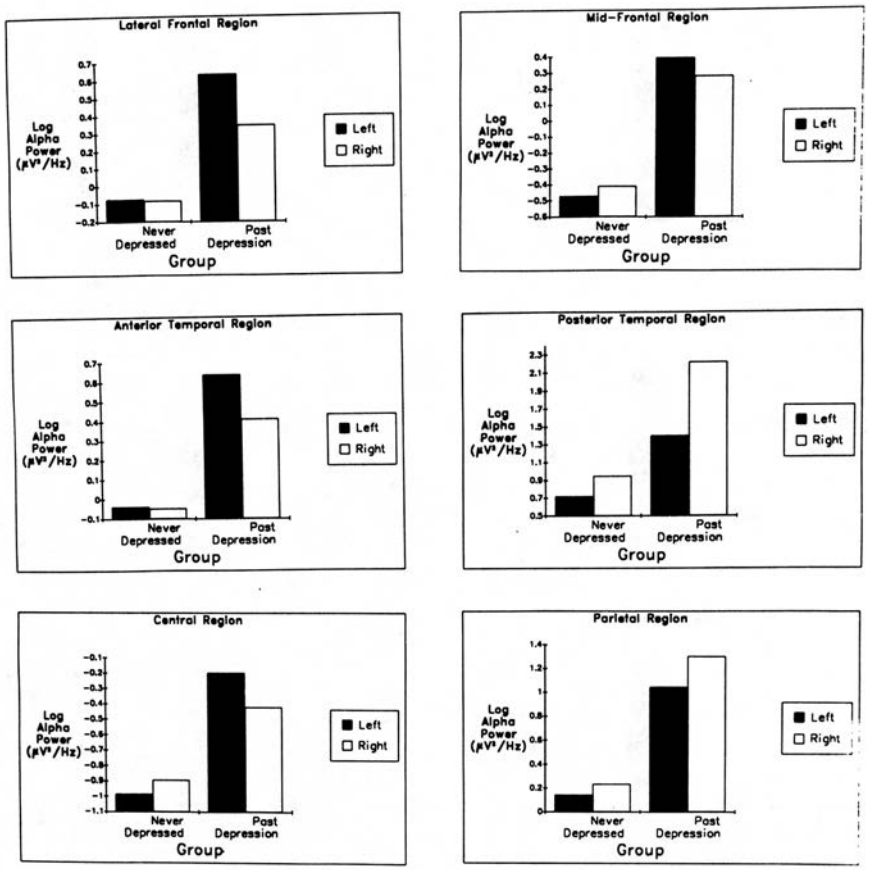

Figure 4. Mean log-transformed alpha (8–13 Hz) power (in $\mu V^2/Hz$) for average-referenced EEG (across eyes-open and eyes-closed baselines), split by group and hemisphere, for each region separately.

two groups did not differ in EMG asymmetry in any region, which justified our use of ANCOVA. All of the previously significant interactions between group and hemisphere remained significant, with the exception of the group difference in posterior temporal asymmetry for the Cz reference.[3] For the uncorrected data, this interaction was significant ($p \leq .05$). When EMG from this site was statistically removed, the p value for the interaction dropped ($p \leq .08$). For all of the other significant interactions, the p value for the corrected data was identical to that for the uncorrected data. Overall, these findings for the EMG-band data indicate that the group differences in asymmetrical alpha power are unconfounded by the presence of slight muscle activity in a small subset of subjects.

Table 3
Mean Log-Transformed Delta Power ($\mu V^2/Hz$) in the Lateral Frontal Region Referenced to Computer-Averaged Ears, for Subjects With and Without a History of Depression

	Group			
	Never depressed		Previously depressed	
Hemisphere	*M*	*SD*	*M*	*SD*
Left	0.747	0.811	0.939	0.558
Right	0.903	0.784	0.798	0.731

Note. Averaged across eyes-closed and eyes-open baselines.

Correlations Between Power and Asymmetry

To investigate the possibility that the observed group differences in alpha asymmetry were not simply the result of differences between the two groups in overall activation, we computed correlations between alpha asymmetry (log R − log L alpha power) and absolute alpha power (log R + log L alpha power) in each region and for each of the three reference montages. None of the 18 correlations computed (3 montages × 6 regions) was statistically significant. The average correlation between total power and asymmetry of power, across region and reference montage, was −.05. To test whether the overall pattern of correlation between total alpha power and asymmetry of alpha power differed from zero, we used the procedure recom-

[3] The ANCOVAs used alpha asymmetry as the dependent variable to avoid the necessity of using multiple covariates (i.e., left and right hemisphere EMG values) for each analysis. When asymmetry is the dependent variable, a main effect for group is equivalent to a Group × Hemisphere interaction (i.e., the F values are the same).

mended by Cohen and Cohen (1983, p. 57) to test the omnibus null. The omnibus test was not significant, $\chi^2(18, N = 14) = 14.74$.

Discussion

Our data indicate that normothymic subjects differing only in their history of depression can be discriminated on the basis of a short sample of resting brain electrical activity. Previously depressed subjects showed less left frontal activation and less right posterior activation than did never-depressed subjects. This general pattern of regional activation asymmetry in the two groups was found for each of the three computed reference montages. The two groups of subjects were carefully matched on age, sex distribution, and socioeconomic status. These subjects did not differ in the amount of depression reported either on the HDRS or on the BDI. Moreover, the two groups did not differ in their self-reported emotional state at the time the EEG data were recorded. This lack of a difference in emotional state between the two groups at the time of testing lends support to our view that these asymmetries reflect stable trait differences.

The differences that we observed cannot be attributed to differences in medication history, as none of our previously depressed subjects had received medication for their past depressions. Another question that might be raised about our results concerns the removal of eye movement artifacts. Although the EEG data were carefully edited to remove all epochs associated with any visually detectable eye movement or blink, it is possible that some EEG activity associated with very small eye movements was included in our analyses. However, the power spectrum of EOG eye movement activity is predominately in the subdelta and delta bands and such activity is negligible for frequencies in the alpha band and above (Gasser, Sroka, & Mocks, 1985). Furthermore, it has been noted that eye movement correction has no effect on asymmetry (Gasser, Sroka, & Mocks, 1986). Thus it is very unlikely that small eye movements, undetectable in the EOG record, influenced our measures of EEG asymmetry.

We wish to note one limitation of our study. The sample size used for each group was small, and some of the group differences that were near-significant might become significant with additional subjects. The fact that the predicted group differences in anterior and posterior alpha power asymmetry were statistically significant even in this small sample size underscores the robust nature of activation asymmetry as a potential biological marker for depression.

In previous work, Davidson (1984, 1987) has suggested that the essential basis for asymmetry in the anterior regions is approach and withdrawal, with the left anterior region specialized for approach and the right anterior region specialized for withdrawal. The diminished left-sided anterior activation that we previously found among depressed subjects has been interpreted to reflect deficits in an approach system. This view is consistent with factor-analytic studies of mood in depressed patients, which suggests that such individuals are characterized primarily by decreased positive affect, not increased negative affect (Tellegen, 1985; Watson, Clark, & Carey, 1988). We have speculated that individuals who display this pattern of asymmetry in the resting state are more vulnerable to certain negative affective states and depressive disorders, given a certain level of environmental stress. In a number of previous studies, we have found that both infants (e.g., Davidson & Fox, 1989) and adults (e.g., Tomarken et al., 1988; see review in Davidson & Tomarken, 1989) with different patterns of baseline activation asymmetry react differently to affect elicitors. For example, Davidson and Fox (1989) have reported that 10-month-old infants with less left frontal activation at rest are more likely to cry in response to a brief episode of maternal separation than are infants showing the opposite pattern of asymmetry. We view decreased left anterior activation as a diathesis that lowers the threshold for triggering emotions and psychopathology associated with deficits in approach (i.e., sadness and depression). We (Davidson & Tomarken, 1989) previously proposed that individuals with accentuated right-sided anterior activation (in contrast to deficient left-sided anterior activation) are specifically vulnerable to withdrawal-related emotion and psychopathology (e.g., fear, disgust, and anxiety disorders).

The diminished right-sided posterior activation we have observed in previously depressed subjects is similar to that found among currently depressed subjects (Davidson et al., 1987; Tucker, 1981). We have suggested that this pattern of posterior asymmetry is associated with the selective spatial cognitive deficits that have been reported to accompany depression (Davidson et al., 1987; Tucker & Frederick, 1989). Moreover, the deficit in right-sided posterior activation may directly contribute to certain symptoms of depression, such as poor orienting and deficits in social skills, which require the decoding of nonverbal, expressive behavior. The degree to which the anterior and posterior asymmetries co-occur, or rather, represent separate subgroups with different etiologies, remains to be explored in future research. It should be noted that in several previous studies, we observed inverse relations between frontal and parietal asymmetry in depressives (e.g., Davidson et al., 1985; Davidson et al., 1987).

The discrimination we found between previously depressed and never-depressed subjects was based on only a 1-min sample of EEG. Whereas a sample of this length may appear short, it should be noted that stable estimates of EEG power spectra can be obtained with samples as short as 20 s (Gasser, Bacher, & Steinberg, 1985; Mocks & Gasser, 1984). Measures of regional brain electrical asymmetry may therefore provide a very economical index of vulnerability to affective disorders.

The fact that remitted depressives can be discriminated from never-depressed subjects has important implications for the composition of control groups in studies of psychopathology. Our data suggest that control subjects must be screened for lifetime history of psychopathology. If currently normothymic but previously ill control groups are used, it is less likely that differences between psychiatric and putatively normal groups will be found. Investigators who have studied neuroanatomical correlates of affective disorders have also underscored the importance of the composition of the control group in determining the outcome of studies (see Depue & Iacono, 1989, for review).

This study incorporated several methodological advances not normally included in studies of quantitative electrophysiology. In addition to an examination of all frequency bands, we examined the EEG using three different reference montages and found that the Group × Region × Hemisphere interaction for alpha power was consistent across all three referencing procedures. Moreover, we computed power in a high-frequency band

that was presumably influenced purely by myogenic and not neurogenic activity. Power in this band provided a measure of muscle contamination. Using activity in this band as a covariate, we found that virtually all of the significant effects in alpha power remained significant, which indicated that the group differences in alpha asymmetry were not artifacts of group differences in muscle activity.

These findings suggest that regional activation asymmetries are state-independent. Whether the pattern of diminished left-sided anterior and right-sided posterior activation that we found in the previously depressed subjects actually predicts vulnerability to depression, rather than reflects changes in activation subsequent to depression, is a question that must await future longitudinal research.

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