Electroencephalographic Measures of Regional Hemispheric Activity in Offspring at Risk for Depressive Disorders

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Background: *Electroencephalographic (EEG) studies have found abnormal regional hemispheric asymmetries in depressive disorders, which have been hypothesized to be vulnerability markers for depression. In a longitudinal high-risk study, resting EEG was measured in primarily adult offspring of depressed or nondepressed probands.*

Methods: *Electroencephalograms from12 homologous sites over each hemisphere (digitally linked-ears reference) were analyzed in right-handed offspring for whom both parents (n = 18), one parent (n = 40), or neither parent (n = 29) had a major depressive disorder (MDD).*

Results: *Offspring with both parents having MDD showed greater alpha asymmetry at medial sites, with relatively less activity (more alpha) over right central and parietal regions, compared with offspring having one or no parent with MDD. Relatively less left frontal activity at lateral sites was associated with lifetime MDD in offspring but not with parental MDD. Offspring with both parents having a MDD also showed markedly greater anterior-to- posterior increase in alpha with eyes closed compared with those with one or no parent with a MDD.*

Conclusions: *Alpha asymmetry indicative of right parietotemporal hypoactivity, previously reported for depressed adolescents and adults, and heightened anterior-to-posterior gradient of alpha are present in high-risk offspring having parents concordant for MDD.*

Key Words: Alpha power, EEG, hemispheric asymmetry, high risk, major depressive disorder

Studies have consistently shown that offspring of depressed parents are at increased risk for major depressive disorder (MDD), anxiety disorders, and comorbidity of these disorders (Hammen et al 1990; Warner et al 1995; Weissman et al 1987, 1997). Given the likelihood of childhood onset of these disorders (Puig-Antich et al 1989; Weissman et al 1988, 2005; Williamson et al 1995), the development of markers for identifying children at risk for depressive or anxiety disorders is of key importance. A convergence of evidence has suggested that electroencephalographic (EEG) measures of frontal brain asymmetry, which are noninvasive and readily obtained in young children, are good candidates as neurophysiologic markers of vulnerability to depressive or anxiety disorders. This includes EEG studies in 1) infants of depressed mothers (Dawson et al 1997; Field et al 1995), 2) behaviorally inhibited children (Davidson and Fox 1989; Fox et al 1992), and 3) adults with a history of childhood-onset depression (Miller et al 2002). Davidson (1992) proposed a model in which asymmetry of frontal brain activity identifies a diathesis predisposing individuals to respond with predominately negative or positive affect. Reduced left-frontal activation is hypothesized to be associated with a deficit in approach-related behaviors or positive affect, and right frontal activation is hypothesized to be associated with withdrawal-related behaviors or negative affect.

The primary EEG measure of regional hemispheric activity has been alpha power because of its inverse relation to cortical activity (Shagass 1972). Alpha power is maximum when subjects are in a restful, awake state with their eyes closed. Conversely, increases in cortical activity (e.g., during eyes opening or visual stimulation) are associated with a decrease in alpha power. Early studies measuring resting EEG reported higher alpha power with eyes closed and greater alpha suppression with eyes open in depressed patients when compared with control subjects (Pollock and Schneider 1990; Shagass et al 1988). More recent studies have focused on abnormalities of regional hemispheric asymmetries, as measured by EEG alpha power over left and right hemisphere sites. Based on the assumption of an inverse relation of alpha power to cortical activity, we refer here to cortical activity rather than alpha power. Infants of depressed mothers who are at risk for depressive disorders exhibited reduced activity over the left frontal region compared with infants of nonsymptomatic mothers (Dawson et al 1997; Field et al 1995). Behaviorally inhibited children showed an alpha asymmetry indicative of greater right than left frontal activity, whereas uninhibited children showed the opposite asymmetry (Davidson and Fox 1989; Fox et al 1992). Depressed adults have also been reported to show greater right than left frontal activity (Bell et al 1998; Davidson et al 1987; Gotlib et al 1998; Henriques and Davidson 1991), but not all studies have found this frontal asymmetry (Reid et al 1998). Some studies have found the opposite alpha asymmetry at posterior sites in depressed adolescents and adults, with relatively less activity over right parietal sites (Bruder et al 1997; Davidson et al 1987; Kentgen et al 2000; Reid et al 1998), but other studies have not found this asymmetry (Henriques and Davidson 1991). Inconsistent alpha asymmetry findings for depressed patients have been related to comorbidity with anxiety disorders, clinical heterogeneity of depression, differences in reassurance-seeking, methodologic differences, or instability of alpha asymmetry (Bruder et al 1997; Davidson 1998;

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Received March 10, 2004; revised November 3, 2004; accepted November 9, 2004.

0006-3223/05/$30.00
doi:10.1016/j.biopsych.2004.11.015

Debener et al 2000; Heller et al 1995; Heller and Nitschke, 1998; Minnix et al 2004; Reid et al 1998).

These EEG studies, together with evidence of abnormal cognitive laterality in depressed adults (Bruder 2003) and mood disorders following unilateral lesions in stroke patients (Shimoda and Robinson 1999), support the hypothesis that both left frontal and right parietotemporal hypoactivity are involved in depressive disorders (Heller and Nitschke 1997; Kinsbourne and Bemporad 1984). Heller and Nitschke (1997) interpreted deficits in left frontal and right parietotemporal activity in depression in terms of their two-dimensional model of emotions. A "valence" dimension of emotion was hypothesized to involve frontal systems, with pleasant or positive emotions associated with left frontal activity and unpleasant or negative emotions associated with right frontal activity, and an "arousal" dimension was hypothesized to involve a right posterior system. Depression was thought to be characterized by relatively greater right than left frontal activity associated with unpleasant affect and decreased right parietotemporal activity associated with low emotional arousal. Left frontal and right parietal hypoactivity in remitted depressed patients who were normothymic during EEG testing suggested that abnormalities of alpha asymmetry may represent state-independent, trait markers of vulnerability to depression (Henriques and Davidson 1990).

As part of a longitudinal high-risk study in offspring of depressed or nondepressed probands (Warner et al 1999; Weissman et al 1997), resting EEG was measured in a subsample of offspring who had been followed since childhood or adolescence and were now primarily adults. The aim was to evaluate the potential usefulness of EEG alpha asymmetry measures as biological markers of a phenotype of depression characterized by familial loading for MDD. Based on the EEG findings described earlier, it was hypothesized that frontal alpha asymmetry would vary as a function of familial loading of MDD and lifetime diagnosis of MDD in offspring. Specifically, high-risk offspring of depressed parents will show relatively greater right than left frontal activity, whereas low-risk offspring having no parental MDD will not show this alpha asymmetry. Similarly, given findings of abnormal posterior alpha asymmetry in adolescent and adult depression (Bruder et al 1997; Henrigues and Davidson 1990; Kentgen et al 2000; Reid et al 1998), high-risk offspring may also differ from low-risk offspring in showing relatively less right posterior activity. In a prior report (Nomura et al 2001), offspring of parents concordant for MDD had the highest risk for MDD, anxiety disorder, and alcohol dependence. We therefore compared the EEG of offspring in three groups having: 1) both parents with MDD, 2) one parent with MDD, or 3) neither parent with MDD. Offspring whose both parents have an MDD were expected to show the greatest difference in alpha asymmetries compared with low-risk offspring having neither parent with depression. Moreover, availability of lifetime diagnoses for offspring in this longitudinal study also made it possible to examine the relation of alpha asymmetries to diagnosis of MDD.

Methods and Materials

Subjects

Offspring were originally selected for the presence or absence of lifetime history of MDD in their parents. The probands with MDD had received treatment for mood disorders in outpatient clinical research settings at Yale University. The control probands came from a community survey that was conducted in New Haven, Connecticut, and had no lifetime history of psychiatric illness based on several direct interviews (see Warner et al 1999; Weissman et al 1982, 1992, 1997). Assessments of offspring and parents were conducted at baseline (Wave 1), 2 years later (Wave 2), and 10 years later (Wave 3). A fourth wave of assessments was obtained about 20 years after baseline (see-Weissman et al 2004, 2005). The lifetime diagnoses for offspring in this report are based on extensive interviews concerning medical, psychiatric, and social functioning, as well as medical records when available at all four waves over 20 years on the offspring and their parents. Probands, spouses and offspring were independently interviewed using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) for adults (Mannuzza et al 1986), and for children between ages 6 and 17, the child version (K-SADS-E; Orvaschel et al 1982) modified for DSM-IV at Wave 4 (K-SADS-PL; Kaufman et al 2001) was used. Diagnostic assessments of offspring were conducted by mental health professionals with doctoral or masters degrees who received intensive training for interrater reliability and were blind to the clinical status of the parents (Weissman et al 1997). Multiple sources of information were obtained, including independent assessments of offspring by direct interview, parent report, and direct assessment of both biological parents as often as possible. Diagnoses were based on the best estimate procedure (Leckman et al 1982). A child psychiatrist and child psychologist, who were not involved in the interviewing, independently and blind to the diagnosis of the parent and to prior assessments reviewed all the material and assigned a DSM-IV diagnosis. The lifetime diagnoses were cumulative across all four waves over 20 years and using DSM-IV criteria at the definite level. The clinical and electrophysiologic assessments were approved by the New York State Psychiatric Institute/Columbia University Institutional Review Board and informed consent was obtained.

Electrophysiologic tests were obtained during the fourth wave of assessments when most of the offspring were adults. The tests included resting EEG followed by startle response measurements (Grillon et al, in press). To be eligible for these tests, the offspring had to be over 7 years old, living in the geographic area of the study, and without a hearing impairment or history of seizures, epilepsy, head trauma, or psychosis. Of the182 second-generation offspring who were eligible, EEG was recorded in 111. Six of these offspring did not have useable EEG data, and 18 were not right-handed by self-report. The EEG data for the remaining 87 right-handed offspring with sufficient artifact-free data are presented in this report. Of these offspring, 18 (10 female, 8 male subjects) had two parents with MDD, 40 (25 female, 15 male subjects) had one parent with a MDD, and 29 (18 female, 11 male subjects) were offspring of nondepressed control subjects. Although the offspring were followed since childhood or adolescence, at the time of EEG measurements, the mean age of offspring having two depressed parents (M = 29.0, SD = 11.0, range 8–47 years) was less than those having one depressed parent (M = 37.0, SD = 8.0, range 22–50) or neither parent depressed (M = 37.1, SD = 4.7, range 29–47) (F = 7.60, df = 2, 84, $p < .001$). This difference was due to the presence of four offspring with two depressed parents who were between 8 and 18 years of age, whereas those in the other two groups were all adults. There was no significant difference in age among the three groups after these four offspring were excluded from the analysis. The EEG data when they were excluded were essentially the same as those reported later for the full samples. Also, age of offspring was not significantly correlated with alpha asymmetry at lateral frontal (r = .02, ns) or medial parietal (r =

–.21, ns) sites, where differences in alpha asymmetry were observed in this study. Among offspring who had a lifetime diagnosis of MDD, those with two depressed parents tended to have an earlier age of onset (M = 14.0, SD = 11.2) compared with those with one depressed parent (M = 22.0, SD = 10.4) or neither parent depressed (M = 19.4, SD = 5.3), but this difference was not statistically significant ($F = 2.03$, $df = 2,38$, $p = .14$).

Table 1 gives the percentage of offspring in the three groups who had lifetime diagnoses of MDD, anxiety disorders, and other disorders. The offspring with MDD in one or both parents had higher lifetime rates of MDD, anxiety disorders and phobias compared with those with neither parent depressed. Although higher lifetime rates of depressive and anxiety disorders in these high-risk offspring are in accord with Wave 3 assessments in the full sample (Nomura et al 2001), offspring with MDD in both parents did not show higher rates of disorders than those with MDD in one parent. The data in Table 1 are based on Wave 4 assessments of less than half of the eligible offspring in the sample. The rates of psychiatric disorders for offspring in these three groups did not, however, differ systematically from those for the full sample of second generation offspring interviewed at 4 Waves.

Procedures

Resting EEG was measured while subjects sat quietly during four 2-min periods, with the order of the eyes open or closed conditions counterbalanced across subjects (eyes open, closed, closed, open or closed, open, open, closed). Subjects were instructed to remain still and to blink or move their eyes or body as little as possible during the recording periods. In the eyes-open condition, subjects fixated on a cross centered on a computer monitor.

Scalp EEG was measured from 12 electrodes over medial and lateral frontal, central, and parietal regions with half at homologous sites over each hemisphere (F3, F4; F7, F8; C3, C4; T7, T8; P3, P4; P7, P8) using an electrode cap (Electro Cap International, Eaton, OH) with a left ear reference. Tin electrodes were placed on the right ear, as well as at supra- and infraorbital sites surrounding the right eye to monitor eye blinks and vertical eye movements (bipolar) and at right and left outer canthi to monitor horizontal eye movements (bipolar). The EEGs were subsequently re-referenced digitally to a linked-ears reference. All electrode impedances were below 5 Ω. The EEGs were recorded using a Bioamplifier system (James Long Company, Caroga Lake, New York) at a gain of 10 K (5 K for eye channels), with a band pass of .01–30 Hz. A PC-based EEG acquisition system (NeuroScan, Sterling, Virginia) acquired and digitized the data continuously at 200 samples/sec during each recording period.

EEG Analyses

The EEG data were segmented into consecutive 1.28-sec epochs every .64 sec (50% overlap). Epochs contaminated by blinks, eye movements, or movement-related artifacts were excluded using a rejection criterion of ± 100 μv on any channel, followed by interactive rejection of remaining artifacts. The DC offset of each epoch was removed, and the EEG was tapered over the entire 1.28 sec using a Hanning window to suppress spectral side lobes (Bendat and Piesol 1971). The Hanning window de-emphasizes data near the beginning and end of each epoch. By overlapping the epochs by 50%, the attenuated data are restored in adjacent epochs, preserving data with minimal redundancy. The EEG data were subjected to an offline power-spectrum analysis using a Fast Fourier Transform. Analyses focused on the alpha band, where prior studies have found differences in hemispheric asymmetries for depressed subjects (Bruder et al 1997; Henriques and Davidson 1990, 1991; Kentgen et al 2000). At each electrode, alpha power was averaged for artifact-free epochs spanning each recording period for each condition, and subsequently integrated over 7.0- to 12.5-Hz band. These alpha band limits were selected after verifying that they adequately sampled the alpha peak for each subject. Logarithms of alpha power were then computed to normalize the data. Secondary analyses of power in the delta (0–3.9 Hz), theta (4–6.9 Hz), and low-beta (13–19.5 Hz) frequency bands were also conducted to determine whether group differences in hemispheric asymmetry for alpha were also evident for these bands. The total number of minutes of artifact-free EEG data did not differ significantly among the groups with MDD in both parents (M = 6.3, SD = 1.3), one parent (M = 5.6, SD = 1.3), or neither parent (M = 6.0, SD = 1.3; $F = 1.59$, $df = 2,84$, $p = .21$), or between offspring having a lifetime diagnosis of MDD (M = 5.8, SD = 1.3) and those with no MDD (M = 6.0, SD = 1.3; $F = .47$, $df = 1, 85$, $p = .49$).

Statistical Analyses

The log power measures at each electrode were submitted to a repeated-measures analysis of variance (ANOVA) using four within-subject factors: Hemisphere (left, right), Anterior–Posterior (frontal, central, parietal), Medial–Lateral, and Condition (eyes open, eyes closed). Two between-subject or group factors were Parental MDD (neither, one, or two parents having MDD)

Table 1. Rates of Lifetime Disorders in Offspring Based on Parental MDD Status

	Parental MDD Status				
	Neither	One	Both		
Number of Offspring	29	40	18		
Diagnoses in Offspring	*N* (%)	*N* (%)	*N* (%)	χ^2	*p*
Anxiety Disorder	5 (17.2)	24 (60.0)	11 (61.1)	14.47	**.0007**
Phobia	3 (10.3)	17 (42.5)	10 (55.6)	12.15	**.002**
MDD	8 (27.6)	25 (62.5)	8 (44.4)	8.29	**.015**
Conduct Disorder	5 (17.2)	15 (37.5)	3 (16.7)	4.66	.10
Disruptive Disorder	5 (17.2)	16 (40.0)	4 (22.2)	4.72	.09
Alcohol Abuse/Dependence	7 (24.1)	12 (30.0)	1 (5.6)	4.22	.12
Drug Abuse/Dependence	7 (24.1)	9 (22.5)	2 (11.1)	1.30	.52
Attention-Deficit Disorder	1 (3.4)	5 (12.5)	1 (5.6)	2.05	.36
Dysthymia	6 (20.7)	8 (20.0)	4 (22.2)	.04	.98

MDD, major depressive disorder. Bold face *p* values indicate significant correlation.

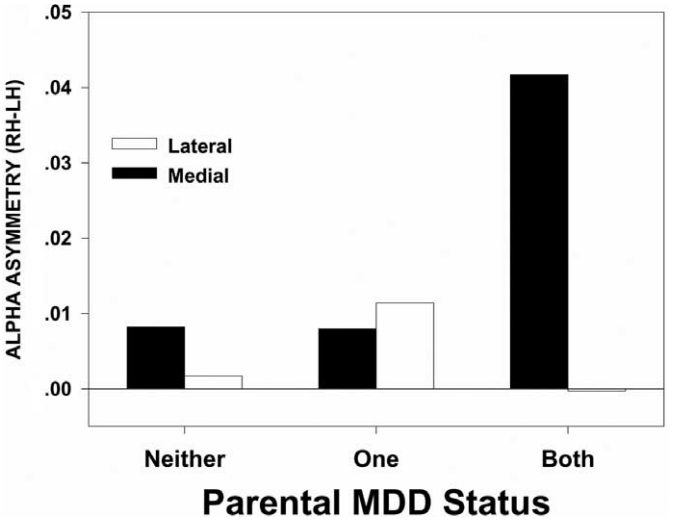

Figure 1. Mean alpha asymmetry (difference between right [RH] and left hemisphere [LH] log alpha power) at lateral and medial sites (averaged over anterior–posterior regions) for offspring with neither, one, or both parents having major depressive disorder (MDD).

and MDD Diagnosis in offspring (absent or present). When significant interactions involving group, hemisphere, and the other topographic factors were found, subsequent analyses followed up on these group differences in hemispheric asymmetry by restricting analyses to medial and lateral electrode sites for each region. *F* ratios were evaluated using degrees of freedom computed with the Greenhouse–Geisser ϵ correction (Jennings and Wood 1976) where appropriate to counteract heterogeneity of variance–covariance matrices with repeated measures. Secondary analyses were also conducted using the same repeated-measures ANOVA to examine the specificity of differences in alpha asymmetry between groups by examining delta, theta, and low-beta frequency bands.

Results

ANOVA of alpha power indicated that differences in alpha asymmetry (i.e., right – left hemisphere log alpha power) as a function of parental MDD were dependent on the Medial–Lateral location of the electrode sites (Parental MDD × Hemisphere × Medial–Lateral interaction; $F = 3.14$, $df = 2,81$, $p < .05$). Figure 1 shows the alpha asymmetry at medial and lateral sites (averaged over Anterior–Posterior regions) for offspring with neither, one, or both parents having a MDD. More positive asymmetry scores indicate relatively less activity (greater alpha) over the right hemisphere. Offspring with both parents having a MDD showed markedly greater alpha asymmetry at medial sites, indicating relatively less right hemisphere activity, compared with offspring with only one or no parent with MDD (Parental MDD × Hemisphere interaction; $F = 4.16$, $df = 2,81$, $p < .05$). In contrast, there was no significant difference in alpha asymmetry among these groups at lateral sites ($F = .80$, $df = 2,81$, $p = .45$). The difference in alpha asymmetry at medial sites among offspring differing in parental MDD was present whether or not they had a lifetime diagnosis of MDD, that is, there was no significant interaction between MDD Diagnosis in offspring and Hemisphere ($F = .87$, $df = 1,81$, $p = .35$) or among MDD Diagnosis, Parental MDD, and Hemisphere ($F = .23$, $df = 2,81$, $p = .79$). Moreover, additional analyses using lifetime diagnosis of an anxiety disorder in offspring as a grouping variable (instead of MDD Diagnosis) indicated that there was also no significant interactions involving Anxiety Disorder diagnosis in offspring and hemispheric asymmetry of alpha at medial or lateral sites. Thus, the presence of a lifetime diagnosis of MDD or anxiety disorder in offspring did not affect the relation of parental MDD to alpha asymmetry. The higher-order interaction involving Parental MDD, Hemisphere, Medial–Lateral, and Anterior–Posterior electrode location approached statistical significance ($F = 2.22$, $df = 4,162$, $\epsilon = .90$, $p = .08$). Our a priori hypotheses concerning group differences in alpha asymmetry in frontal or posterior regions led us to further examine whether the asymmetry differences at medial sites were dependent on the Anterior–Posterior dimension. As is evident in Figure 2, greater alpha asymmetry in offspring with both parents having an MDD compared with the other groups (Parental MDD × Hemisphere interaction) was present at medial central ($F = 3.16$, $df = 2,81$, $p < .05$) and parietal ($F = 3.71$, $df = 2,81$, $p < .05$) sites, but not at frontal sites ($F = .29$, $df = 2,81$, $p = .75$).

There were differences in alpha asymmetry between offspring differing in lifetime diagnosis of MDD, which were dependent on both Medial–Lateral and Anterior–Posterior electrode location (MDD Diagnosis × Hemisphere × Medial–Lateral × Anterior–Posterior interaction: $F = 3.46$, $df = 2,162$, $\epsilon = .90$, $p < .05$). This interaction reflects the significant difference in alpha asymmetry between offspring with versus without a MDD at lateral but not medial frontal sites (MDD Diagnosis × Hemisphere × Medial–Lateral interaction: $F = 8.84$, $df = 1,81$, $p < .01$), which was not present at central or parietal sites. Figure 3 shows the alpha asymmetry for each group at lateral and medial sites over frontal, central and parietal locations. At lateral sites, offspring having a diagnosis of MDD showed relatively greater activity (less alpha) over the right frontal site, whereas offspring without MDD showed essentially no frontal alpha asymmetry (MDD Diagnosis × Hemisphere interaction: $F = 6.90$, $df = 1,81$, $p = .01$). In contrast, there was no difference in alpha asymmetry between these groups at lateral central ($F = .56$, $df = 1,81$, $p = .34$) or parietal ($F = .01$, $df = 1,81$, $p = .90$) sites, or at medial frontal, central or parietal sites (all *F* values ≤ 1.16, $p \geq .28$).

There were no significant differences in overall alpha power among offspring differing in parental MDD or diagnosis of MDD. There were, however, marked differences in their topographic

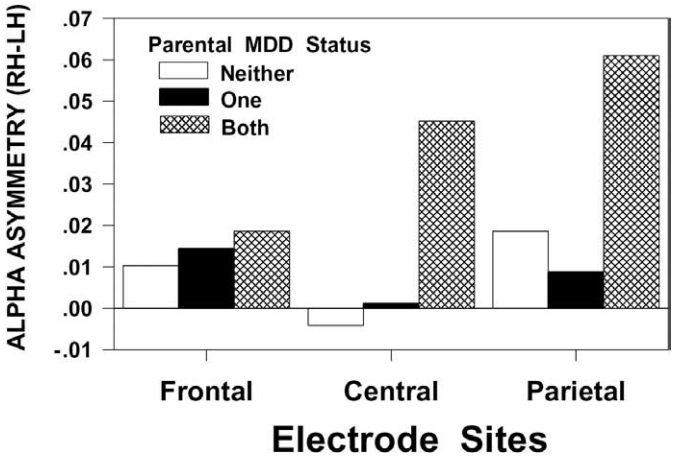

Figure 2. Mean alpha asymmetry (difference between right [RH] and left hemisphere [LH] log alpha power) at medial frontal, central, and parietal sites for offspring with neither, one, or both parents having an major depressive disorder (MDD).

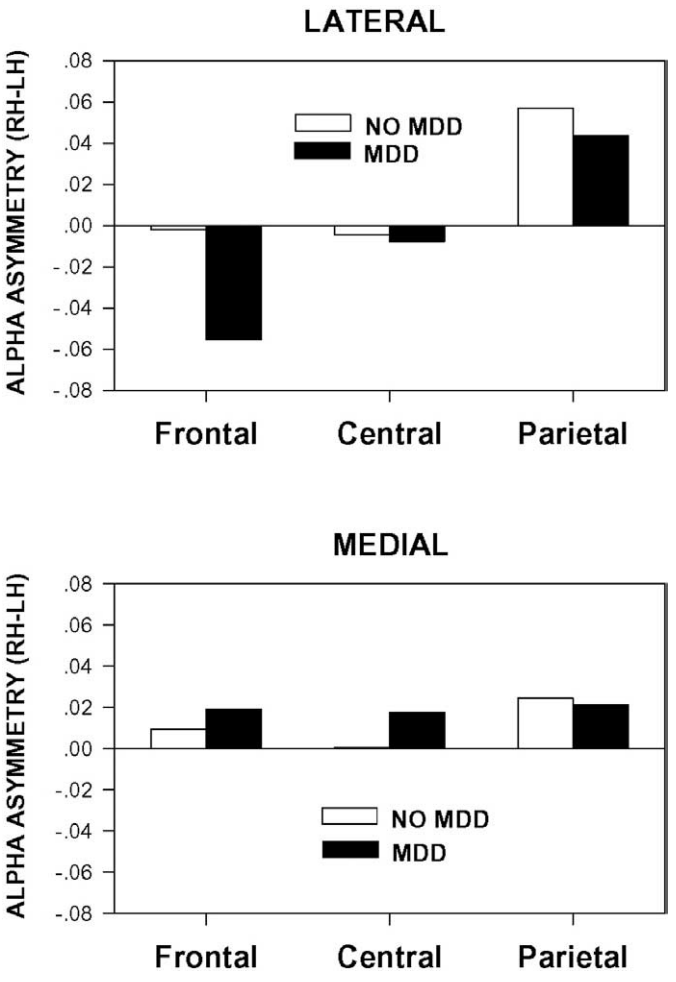

Figure 3. Mean alpha asymmetry (difference between right [RH] and left hemisphere [LH] log alpha power) at lateral and medial frontal, central, and parietal sites for offspring with or without a lifetime diagnosis of major depressive disorder (MDD).

gradient of alpha, that is, increase in log alpha power from anterior to posterior sites. Figure 4 shows the alpha gradient (parietal minus frontal log alpha power) in eyes open and closed conditions for offspring differing in parental MDD (right portion) or lifetime diagnosis of MDD (left portion). The alpha gradient was greatest in the eyes closed condition where alpha power is largest (Anterior-Posterior × Condition interaction: $F = 109.36$, $df = 2, 162$, $\epsilon = .61$, $p < .0001$). Figure 4 illustrates the three-way interactions between Parental MDD × Anterior–Posterior × Condition ($F = 9.32$, $df = 4, 162$, $\epsilon = .61$, $p < .001$) and between MDD Diagnosis × Anterior–Posterior × Condition ($F = 8.49$, $2,162$, $\epsilon = .61$, $p < .005$). These interactions reflect the difference in alpha gradient among groups in the eyes closed but not eyes open condition. As shown in right portion of Figure 4, alpha gradient with eyes closed was greater for offspring with both parents having a MDD than in the other groups (Parental MDD × Anterior–Posterior interaction: $F = 5.55$, $df = 4,162$, $\epsilon = .64$, $p < .005$). Newman–Keuls post hoc tests indicated that alpha gradient was significantly greater in offspring with both parents having a MDD than in those with one or neither parent having a MDD ($p < .05$), but there was no significant difference between the latter groups. The left portion of Figure 4 also shows that offspring having a diagnosis of MDD had a greater alpha gradient with eyes closed compared with those without MDD (MDD Diagnosis × Anterior–Posterior interaction: $F = 5.95$, $df = 2,162$, $\epsilon = .64$, $p = .01$). There was, however, no higher-order interaction involving both Parental MDD and MDD Diagnosis, which indicates that the greater increase in alpha power in offspring with both parents having MDD was not dependent on having MDD.

An ANOVA of power in the delta, theta, and low-beta frequency bands indicated that there were no differences in asymmetry among groups differing in parental MDD. The difference in asymmetry at lateral frontal sites between offspring differing in lifetime diagnosis of MDD was, however, present for both the theta and low-beta bands. The four-way interaction seen for alpha power (MDD Diagnosis × Hemisphere × Medial–Lateral × Anterior–Posterior) was significant for both theta ($F = 3.46$, $df = 2,162$, $\epsilon = .73$, $p < .05$) and low beta ($F = 6.58$, $df = 2,162$, $\epsilon = .93$, $p < .005$). There was a significant difference in asymmetry between offspring with versus without a MDD at lateral but not medial frontal sites (MDD Diagnosis × Hemisphere × Medial–Lateral interaction for theta: $F = 6.37$, $df = 1,81$, $p = .01$, and low beta: $F = 14.27$, $df = 1,81$, $p < .001$), which was essentially the same as seen for alpha (Figure 3). Offspring with a diagnosis of MDD showed less theta and low-beta power over the right than left lateral frontal site, whereas offspring without MDD showed little or no asymmetry. Differences in the anterior–posterior gradient as a function of parental MDD or diagnosis of MDD were not seen for these other frequency bands.

Discussion

Offspring of parents who are concordant for MDD differed from those who are not in EEG alpha asymmetry over parieto-

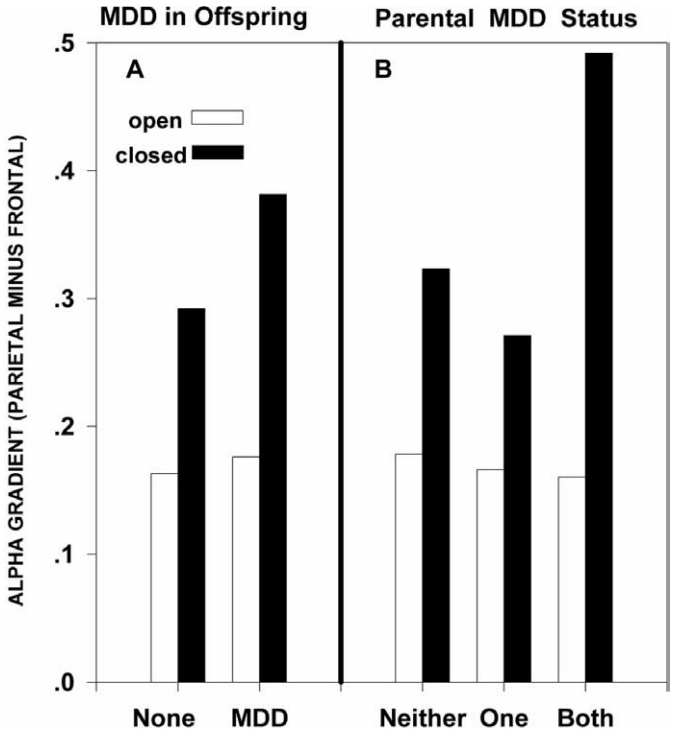

Figure 4. Mean alpha gradient (difference between parietal and frontal log alpha power) with eyes open or closed for offspring with neither, one or both parents having an MDD (right portion of figure) and offspring with or without an MDD (left portion of figure).

temporal regions. The results did not, however, support the hypothesis that asymmetry of frontal activity is a marker of vulnerability to MDD. There was no difference in frontal alpha asymmetry among offspring for whom one, both, or neither parent had a MDD. Alpha asymmetry at central and parietal sites did vary as a function of familial loading of MDD. High-risk offspring, with both parents having a MDD, showed greater alpha asymmetry at medial central and parietal sites compared with those with one or no parents with a MDD. Relatively less right hemisphere activity in offspring having two depressed parents was seen in those with or without a lifetime diagnosis of MDD, which indicates that it is not dependent on the presence of a current depressive disorder. This is consistent with EEG evidence of right parietotemporal hypoactivation in adolescents and adults having a depressive disorder (Bruder et al 1997; Davidson et al 1987; Kentgen et al 2000; Ried et al 1998) and in previously depressed, normothymic adults (Henriques and Davidson 1990). These findings support the hypothesis that reduced right parietotemporal activity is a trait marker of vulnerability to MDD.

Heller et al (1995) reviewed evidence from cognitive-laterality, EEG, and neuroimaging studies suggestive of decreased right parietotemporal activity in depression. Their two-dimensional model of emotion hypothesizes that right parietotemporal activity is associated with both autonomic and behavioral aspects of arousal. The relatively less right parietotemporal activity in offspring with both parents having a MDD may therefore be indicative of low emotional arousal. The right posterior region has also been linked to processing of emotional stimuli, with depressed patients showing evidence of abnormal brain potentials in this region during the processing of emotional stimuli (Deldin et al 2000; Kayser et al 2000). Low positive emotionality in children, which has been has been related to maternal history of depression and may be a risk factor for depression, was found to be associated with an alpha asymmetry indicative of reduced right posterior activity (Shankman et al, in press). Heightened risk for development of a depressive disorder in individuals with reduced right parietotemporal activity may therefore be related to the presence of low emotional arousal and abnormal processing of emotional information.

Offspring with both parents having a MDD also differed from those with one or no parent with MDD in showing greater anterior–posterior alpha gradient with eyes closed. Alpha power is known to be greatest at posterior sites in a resting, eyes closed condition, and it has therefore been suggested to reflect the relative inactivation or idling of cortical neurons. Depressed patients have been reported to show abnormally large alpha with eyes closed and greater reduction of alpha to eyes opening (Pollock and Schneider 1990; Shagass et al 1988), which has been viewed as a reflection of lower than normal activity in depressed patients. Elevated alpha power has also been found in recovered depressed adults in a euthymic state (Pollock and Schneider 1989), which led Pollock and Schneider (1990) to hypothesize that it may reflect a trait difference in a subgroup of depressed individuals with family histories of affective disorders. Although the offspring of depressed parents in our study did not differ from low-risk offspring in overall level of alpha, the greater anterior–posterior gradient with eyes closed in offspring with parents concordant for MDD may reflect relatively less cortical activity in posterior regions.

Lifetime diagnosis of MDD in offspring was associated with both greater alpha asymmetry at lateral frontal sites (F7–F8) and a steeper alpha gradient with eyes closed compared with those without a MDD. The direction of this alpha asymmetry, with relatively greater right frontal activity, is consistent with frontal asymmetry previously reported for depressed adults (Bell et al 1998; Davidson et al 1987; Henriques and Davidson 1991; Gotlib et al 1998). Unlike studies in depressed adults, this alpha asymmetry was not seen at medial frontal sites (F3–F4). Moreover, it was not specific to alpha, but was also present for neighboring theta and low-beta frequency bands, which raises questions about the interpretation of this frontal asymmetry. We also found no evidence of an association between parental MDD and frontal alpha asymmetry, which is at odds with findings for infants of depressed mothers (Dawson et al 1997; Field et al 1995). Most of the offspring in our study were adults, and our findings therefore are not directly comparable to those for infants. Concerns have been raised about the stability of frontal alpha asymmetry (Debener et al 2000; Reid et al 1998) and the need for repeated measurements of resting EEG to provide evidence of stable, trait-related asymmetries (Davidson 1998). There are also a host of variables that may moderate or mediate the relation between frontal alpha asymmetry and depression or risk for depression (Allen and Kline 2004). Studies in healthy adults and children of depressed mothers have identified a number of variables related to individual differences in frontal alpha asymmetry. Most notably, temperament (Reid et al 1998), personality traits of positive and negative affectivity (Tomarken et al 1992), behavioral activation or inhibition (Sutton and Davidson 1997), breast-feeding or other mother–infant interactions (Jones et al 2004), and socioeconomic status (Tomarken et al 2004) need further study in this context.

In accord with prior assessments in this longitudinal study (Nomura et al 2001), the subsample of offspring in our study with parents concordant for MDD had elevated risk for MDD and anxiety disorders compared with offspring with no parental MDD. The subsample of offspring having two parents with MDD did not, however, show greater rates of MDD or anxiety disorders than those with one depressed parent. They did differ from those with one depressed parent in showing both greater alpha asymmetry at medial parietotemporal sites and greater anterior–posterior gradient of alpha, which suggests that they differ in their biological characteristics. The EEG alterations in offspring having both parents with MDD may represent vulnerability markers for a specific phenotype of depression characterized right parietotemporal hypoactivation and familial loading for MDD.

Lastly, there are some limitations or questions that should be discussed. First, there is evidence that depressive and anxiety disorders may be associated with opposite effects on hemispheric asymmetry in posterior regions (Bruder et al 1997; Heller et al 1995). There was no evidence that the relation of parental MDD and alpha asymmetry was affected by diagnosis of an anxiety disorder in the offspring. We did not, however, have ratings of the anxiety of offspring during the EEG tests and the samples were too small to examine the influence of comorbidity on alpha asymmetry in the offspring. Second, familial loading of MDD and lifetime diagnosis of MDD in offspring were associated with a markedly different patterns of alpha asymmetry. Although having two parents with MDD was associated with relatively less right parietotemporal activity at medial sites, lifetime MDD in offspring was associated with the opposite direction of asymmetry at lateral frontal sites. Also, the asymmetry findings for parental MDD were specific to the alpha band, whereas those for diagnosis of MDD were found for theta, alpha, and low-beta bands. The lack of statistical interactions between parental MDD

and lifetime diagnosis of MDD suggests that the EEG asymmetry findings for them are not related. In terms of Heller et al's (1995) model, asymmetry of frontal and parietotemporal activity are associated with different dimensions of emotional processing (valence and arousal) and may therefore be relatively independent. Third, while standard EEG measures provide an indication of regional brain activity, they have limited spatial resolution and do not identify neural mechanisms that contribute to differences in hemispheric activity. Structural and functional neuroimaging measures are now being obtained in this longitudinal high-risk study to help determine the neurophysiologic mechanisms that underlie alterations of regional hemispheric activity in offspring of depressed parents.

This research was supported by National Institute of Mental Health Grant Nos. MH36197 (MMW) and MH36295 (GEB).

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