Relationship of Resting EEG with Anatomical MRI Measures in Individuals at High and Low Risk for Depression

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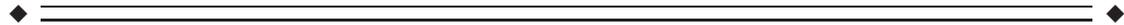
Abstract: Studies have found abnormalities of resting EEG measures of hemispheric activity in depressive disorders. Similar EEG findings and a prominent thinning of the cortical mantle have been reported for persons at risk for depression. The correspondence between EEG alpha power and magnetic resonance imaging (MRI) measures of cortical thickness was examined in a multigenerational study of individuals at risk for depression. Seventy-five participants underwent resting EEG and approximately 5 years later underwent MRI scanning. High-risk participants ($n = 37$) were biological descendants of probands having major depression and low-risk participants ($n = 38$) were descendants of individuals without a history of depression. EEG alpha power was interpolated across the surface of a template brain and coregistered with measures of cortical thickness. Voxel-wise correlations of cortical thickness and alpha power were computed while covarying for age and gender. The high-risk group, when compared to the low-risk group, showed greater alpha asymmetry in an eyes-closed condition, with relatively less activity over right parietal cortex. Alpha power correlated inversely with cortical thickness, particularly over the right posterior region, indicating that EEG evidence of reduced cortical activity was associated with increased cortical thinning. This is the first report of widespread correlation of EEG alpha activity with MRI measures of cortical thickness. Although both EEG and MRI measures are associated with risk for depression, we did not detect evidence that cortical thickness mediated the alpha asymmetry findings. Thus, alpha asymmetry, alone or in combination with MRI, may be a marker of vulnerability for a familial form of depression. *Hum Brain Mapp 00:000–000, 2011.* © 2011 Wiley-Liss, Inc.

Key words: EEG; MRI; cortical thickness; hemispheric asymmetry; high risk; major depressive disorder

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INTRODUCTION

Alpha rhythms in the electroencephalogram (EEG) provide a noninvasive measure of regional cortical activity. Alpha is largest over posterior brain regions in an eyes-closed resting state and is considered an "idling rhythm" that is blocked or diminished by mental activity. Initial neuroimaging studies reported an inverse correlation between EEG alpha power and regional cerebral blood flow in occipital cortex [Sadato et al., 1998]. Studies coregistering EEG and functional MRI have generally confirmed this relationship, with greater alpha power associated with less activity in occipital and parietal lobes [Gonçalves et al., 2006].

Early studies of resting EEG reported overall greater alpha power in depressed patients compared with healthy controls with eyes closed [Pollack and Schneider, 1990; Shagass et al., 1988]. Given the inverse relationship between alpha and cortical activity, greater alpha is assumed to reflect less cortical activity. More recent studies have found abnormal hemispheric asymmetries of alpha in depressed individuals. An alpha asymmetry indicating less left than right cortical activity over frontal sites has been found in depressed adults [Davidson et al., 1987; Gotlib et al., 1998; Henriques and Davidson, 1991], depressed persons having a comorbid anxiety disorder [Bruder et al., 1997], and women who had childhood onset of their depressive illness [Miller et al., 2002]. Several studies have also reported the opposite alpha asymmetry at posterior sites, i.e., relatively less cortical activity over right parietal sites, in depressed adults [Bruder et al., 1997; Davidson et al., 1987; Reid et al., 1998], depressed adolescents [Kentgen et al., 2000], and remitted depressed adults [Henriques and Davidson, 1990]. Studies have provided additional evidence of right parietotemporal dysfunction in depressed patients on neurocognitive tests of lateralized cognitive processing [Bruder, 2003] and on psychophysiologic measures during processing emotional pictures [Deldin et al., 2000; Kayser et al., 2000; Moratti et al., 2008].

Our multigenerational longitudinal study [Weissman et al., 2005] previously reported an alpha asymmetry indicating less right than left parietal activity in family members who were at highest risk for developing a depressive disorder [Bruder et al., 2005, 2007]. Surface EEG measures, however, are limited in their localizing capabilities, leaving unanswered the question of the neural basis for this finding. New anatomical MRI findings from this high-risk study [Peterson et al., 2009] provide independent support for an association between familial risk for depression and asymmetries in parietal cortices. Cortical thickness in high and low risk groups were compared across the cerebral surface. Large expanses of cortical thinning across the lateral aspects of the parietal, posterior-temporal, and frontal cortices of the right hemisphere were found in the high risk group. These convergent findings in the same sample suggest the hypothesis that EEG evidence of relatively less cortical activity over right parietal sites in individuals at high risk for depression may derive from cortical thinning. The availability of both resting EEG and MRI measures in a subsample of subjects in this high-risk study provided a unique opportunity to examine the relation of their EEG alpha and cortical thickness, not only at parietal but also frontal sites where abnormal alpha asymmetry has been found in depression. An additional reason for relating EEG and anatomical MRI measures is that neuropathological processes have been associated with abnormalities of posterior alpha and other EEG rhythms [Babiloni et al., 2008].

METHOD

Participants and Assessments

Probands in Generation 1 (G1) with major depression were originally selected from an outpatient clinic for phar-macologic treatment of depression and had moderate to severe depression with impairment in functioning. Nondepressed controls were recruited from the same community and had no lifetime history of psychiatric illness based on several direct interviews. Full details of clinical assessments at baseline (Wave 1), 2 years later (Wave 2), and 10 years later (Wave 3) have been previously described [Warner et al., 1999; Weissman et al., 1997]. A fourth wave of assessments [Weissman et al., 2005] and electrophyiologic tests ended in 2002. A fifth wave of assessments, which included a partial sample of the second Generation (G2) and third Generation (G3) who agreed to MRI scans, began in 2002 and ended in 2007 [Peterson et al., 2009]. Assessment procedures were kept similar across waves, with few exceptions, to avoid introducing bias from method variation [Weissman et al., 2005]. G1 participants (both probands and nondepressed controls), their spouses, offspring and grandchildren were interviewed independently by mental health professionals who demonstrated high inter-rater reliability on the interview procedures and who were blind to the clinical status of participants in the previous generations. The diagnostic interviews across all waves were conducted using semistructured instruments—the Schedule for Affective Disorders and Schizophrenia Lifetime Version (SAD-L) for adults [Mannuzza et al., 1986] and for children between the ages 6 and 17, the child version [K-SADS-E; Orvaschel et al., 1982] modified for DSM-IV, and at Wave 4, the K-SADS-PL [Kaufman et al., 2001] was used. Lifetime diagnoses using DSM-IV criteria at the definite level were cumulative across all waves for grandparents and their offspring. Grandchildren (G3) were assessed at waves 4 and 5, with a few also at wave 3. 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], which involved an independent review of all assessment materials by two experienced clinicians, a child psychiatrist, and a psychologist, who were not involved in the interviewing and were blind to the diagnostic status of the previous generations and prior assessments.

Resting EEG was obtained during the fourth wave. Offspring or grandchildren who were biological descendents of the G1 probands had to be older than 7 years, live in the geographic area of the study, and have no hearing impairment, history of seizures, head trauma, or psychosis. Of the 182 G2 offspring who were eligible, EEG was recorded in 111. Of the 137 G3 members, 74 participated in the EEG tests. Six of the offspring and seven grandchildren did not have sufficient EEG data, after blink and movement artifact rejection, to be included in this study. The main reason eligible subjects did not participate is that they declined to be tested. Those who did not participate and those who received the electrophysiologic tests did not differ significantly in age, gender, or depression status of the probands. The sample targeted for MRI

TABLE I. Rate of lifetime diagnoses, medications, and demographics in high- and low-risk groups

	High risk (n = 37)	Low risk (n = 38)	P
Diagnoses			
Any anxiety disorder	23 (62.2%)	8 (21.1%)	<0.001[a]
Any phobia	19 (51.4%)	9 (23.7%)	0.013[a]
Major depressive disorder	21 (56.8%)	6 (15.8%)	<0.001[a]
Dysthymia	6 (16.2%)	3 (7.9%)	0.268[a]
Alcohol abuse	7 (18.9%)	4 (10.5%)	0.304[a]
Drug abuse	6 (16.2%)	4 (10.5%)	0.469[a]
Any disruptive disorder	11 (29.7%)	4 (10.5%)	0.038[a]
Medications[b]			
Antidepressants	5 (13.5%)	3 (7.9%)	0.431[a]
Major tranquilizer	0	1 (2.6%)	0.321[a]
Minor tranquilizer	3 (8.1%)	1 (2.6%)	0.291[a]
Gender (female)	20	20	0.902[a]
Right handed	36	37	0.985[a]
Age	33.9 ± 11.7	27.4 ± 13.5	0.028[c]

Means ± SD are shown for age.
[a]χ^2 test.
[b]Within 3 months before EEG.
[c]t test.

scanning in Wave 5 consisted of 196 G2 offspring who were interviewed in Wave 4 and 157 G3 grandchildren who were interviewed in either in Wave 3 or 4. Of these, 150 were scanned and 143 anatomical images were available because 7 were compromised by motion or other scanning artifact. Entry into the MRI scanning also required a negative pregnancy test for females who were postmenarchal and premenopausal and the absence of ferromagnetic implants. Waves 4 and 5 assessments were approved by the Human Investigation Committee at Yale University School of Medicine (where the EEG and MRI scans were performed) and the Institutional Review Board at New York State Psychiatric Institute. This research was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and informed consent was obtained from participants (or parents).

The data for 75 participants (46 G2 and 29 G3) who had both sufficient, artifact-free EEG recordings in Wave 4 and an MRI scan in Wave 5 are presented in this report. Offspring and grandchildren designated as being at "high risk" for depression were biological descendants of G1 probands having a major depressive disorder and those designated at "low risk" were biological descendants of the unaffected controls in G1. The high-risk group included 37 individuals (20 females) and the low-risk group included 38 individuals (20 females). Although high- and low-risk groups did not differ significantly in gender, there was a group difference in age (Table I). The high risk group was somewhat older than the low risk group at the time of the MRI scans and the same was true during EEG tests, when participants were on the average

3.7 years younger (SD = 1.2). All were Caucasian and all but one subject in each group were right-handed based on self-report. Only 9 of the 75 participants received psychoactive medications during the 3 months before the EEG. In the high-risk group, three received an antidepressant, two an antidepressant plus a minor tranquilizer, and one a minor tranquilizer. In the low-risk group, one received an antidepressant, one an antidepressant plus a minor tranquilizer, and one an antidepressant plus a major tranquilizer.[1] Table I also gives the percentage of offspring in the high- and low-risk groups who had lifetime diagnoses of depressive disorders, anxiety disorders, and other disorders. The high-risk group had significantly higher rates of major depression, anxiety disorders, phobias, and disruptive disorders compared with the low-risk group.

EEG Procedures

Resting EEG was measured while subjects sat quietly during four 2-min periods (eyes open, closed, closed, open or eyes 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 recordings. 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 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. The EEG was subsequently re-referenced digitally to a linked-ears reference. Tin electrodes were also placed on the right ear, as well as at supra-and infra-orbital sites surrounding the right eye to monitor eye blinks and vertical eye movements and at right and left

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[1]In a prior study, we found no evidence of any change in alpha power or asymmetry in depressed patients following treatment with the antidepressant fluoxetine [Bruder et al., 2008]. Although samples sizes in the current study are not large enough to examine medication effects, secondary analyses were conducted to determine whether medication could have impacted on the results. First, the EEG alpha power at parietal sites (P3, P4; P7, P8) in eyes closed and eyes open conditions was compared for individuals on versus off psychotropic medications, after collapsing across the high and low risk groups. There was no trend for a Medication Group × Hemisphere or Medication Group × Hemisphere × Condition interaction (P values ≥ 0.53), which suggests that medication had no significant effect on alpha asymmetry at parietal sites. Second, a comparison of cortical thickness between individuals on versus off psychotropic medications showed no significant differences over the broad regions where negative correlations were observed between EEG alpha and cortical thickness. Finally, we found that the critical Risk Group × Hemisphere × Condition interaction for EEG alpha power (see Results) remained significant after excluding the nine individuals who had received psychotropic medications, F = 4.66, df = (1,57), P < 0.05. Thus, the significant difference in condition-related parietal alpha asymmetry between high- and low-risk groups was still observed in individuals who were not on medications.

outer canthi to monitor horizontal eye movements. All electrode impedances were <5 kΩ. EEGs were recorded using a Bioamplifier system (James Long Company, Caroga Lake, NY) at a gain of 10 K (5 K for eye channels), with a band pass of 0.01-30 Hz. A PC-based EEG acquisition system (NeuroScan, Sterling, VA) acquired and digitized the data continuously at 200 samples/sec during each recording period.

Details concerning the analysis of the EEG are given elsewhere [Bruder et al., 2007]. Briefly, artifact-free EEG epochs (1.28 sec every 0.64 sec; Hanning tapered) were submitted to a power spectrum analysis using a Fast Fourier Transform. Analyses focused on the alpha band where prior studies have found differences in hemispheric asymmetry in depressed subjects [Bruder et al., 1997; Davidson et al., 1987; Gotlib et al., 1998; Henriques and Davidson, 1990, 1991; Kentgen et al., 2000; Miller et al., 2002; Reid et al., 1998]. We have found differences between high- and low-risk groups in alpha but not lower or higher frequency bands [Bruder et al., 2005, 2007]. 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. Logarithms of alpha power were then computed to normalize the distribution of the data.

MRI Procedures

Head positioning was standardized using canthomeatal landmarks. Imaging was conducted on a Siemens Sonata 1.5T scanner (Siemens AG) equipped with high-speed gradients (maximum amplification, 40 mT/m; slew rate, 200 mT/m/sec) and running a three-dimensional MP-RAGE sequence (repetition time, 24 msec; echo time, 2.96 msec; 45° flip angle; 256 × 192 matrix; field of view 30 cm; phase field of view = 100%; two excitations, slice thickness 1.2 mm; and 124 contiguous slices encoded for sagittal slice reconstruction with voxel dimensions 1.17 × 1.17 × 1.2 mm).

The brain was isolated from nonbrain tissue by first using Brain Extraction Tool [Smith, 2002] and then manually editing each slice in sagittal, coronal, and axial views. The cortical mantle was defined by applying a global threshold whose value was halfway between the mean gray matter and mean white matter values, and then manually editing this rough classification of cortical gray in all three views [Peterson et al., 2009].

We mapped cortical thickness across cerebral surfaces using procedures previously described [Peterson et al., 2009; Bansal et al., 2005]. Briefly, isolated brains were coregistered using a similarity transformation to an appropriately selected template brain [Plessen et al., 2006]. Each hemisphere of the coregistered brain was normalized to the corresponding hemisphere of the template brain by first a rigid transformation and then a high-dimensional, nonrigid warping based on fluid dynamics, thereby identifying points on the surface of each hemisphere with those on the template surface. From the coregistered brain of each participant, we first subtracted its cortical mantle and

then applied a three-dimensional morphological operator to distance-transform the brain without the cortex [Haralick and Shapiro, 1992; Rosenfeld and Pfaltz, 1968]. This operation calculated cortical thickness as the smallest distance of each point on the external cortical surface from the outermost surface of the white matter in the coregistered brain. Because thicknesses were measured from the coregistered brains that were similarly transformed into the template space, thickness measures inherently account for the generalized scaling effects within the cerebrum. Cortical thickness measures between groups were statistically analyzed and the P values were color encoded and displayed on the high-resolution image of a single individual [Mazziotta et al., 2001]. Finally, on this image we superimposed the manually delineated cortical gyri for better localization of findings.

Normalizing and Coregistering EEG and MRI Data

We normalized EEG data to MRI data using the following procedures. First, electrode sites were interactively registered onto the template brain guided by standard 10-20 placements on the cortical surface [Homan et al., 1987]. Second, each brain was normalized (i.e., coregistered using a similarity transformation and nonlinearly warped) to the template brain, thereby placing the EEG data for each subject into the coordinate space of the template brain. Third, the EEG data from the 12 electrode sites for each subject were interpolated across all voxels on the template surface using a conformal mapping and a method for spherical interpolation. Using the conformal mapping, the surface of the entire brain and the 12 electrode sites were mapped onto a unit sphere. On the unit sphere, the EEG power at the 12 sites was interpolated using the method for spherical splines [parameters: $n = 41$, $m = 2$; Perrin et al., 1989] to compute EEG power at each point on the sphere. The interpolated EEG power was then mapped onto the surface of the entire brain by inverting the conformal mapping. We then correlated at each point on the surface of the two hemispheres the interpolated EEG power with the cortical thickness, while controlling for the confounding variables. Correlating EEG power with the cortical thickness on the brain surface does not imply that we have localized the generators of the alpha power in the cortical mantle. Instead, we interpolated the montage of EEG power measures onto the surface of the brain, rather than on the unit sphere, in order to map the EEG onto the same continuous surface for which we have cortical thickness measures. Probability maps are presented representing the significance of correlations between EEG and cortical thickness at corresponding points on that surface.

Statistical Analyses

Analyses were performed to confirm our published EEG findings for the subsample of offspring and grandchildren
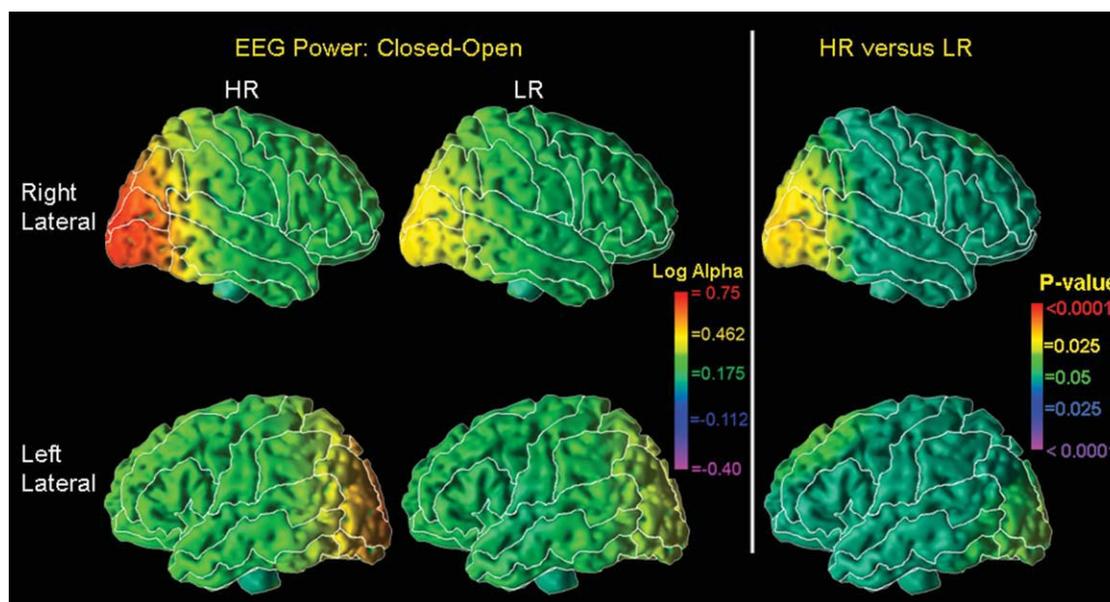
Figure 1.

Left: EEG alpha power (eyes closed-open) mapped onto the cortical surface of each hemisphere in high and low risk groups while covarying for age and sex; Right: power is compared across risk groups at each point of each hemisphere.

who had MRI data. Log alpha power measures for high- and low-risk groups at each electrode site were submitted to an analysis of covariance using Risk group (high vs. low), Generation (2nd vs. 3rd) and Gender as between-subjects factors, and four within-subjects factors: Hemisphere (left vs. right), Region (frontal, central, parietal), Medial-Lateral (F3,4; C3,4;P3,4 vs. F7,8; C7,8; P7,8) and Condition (Eyes open vs. closed). Age was included as a covariate. When a significant interaction involving Risk group, Hemisphere, Region, and Condition was found, subsequent analyses followed up this interaction to determine the significance of group differences in hemispheric asymmetry of alpha for each condition at frontal, central, and parietal regions. F ratios were evaluated using degrees of freedom computed with the Greenhouse-Geisser Epsilon correction [Jennings and Wood, 1976] where appropriate to counteract heterogeneity of variance–covariance matrices with repeated measures.

The coregistration procedures described above were used to map the EEG alpha power measures across the surface of the template brain for each risk group. Student's t-statistics determined the significance of group differences in alpha power at every point on the surface of the template brain while covarying for age and gender, and to compute probability maps. Voxel-wise correlations of cortical thickness and alpha power across the cortical surface were computed while covarying for age, gender, and risk group. Note that including scalp thickness, as measured from the MRI of each participant at the most superior midline site (Cz), as a covariate had essentially no effect

and was therefore not included in the final model. Maps displaying these correlations were corrected for multiple statistical comparisons across the cerebral surface using the false discovery rate (FDR) procedure [Benjamini and Hochberg, 1995], which controls for the expected proportion of false discoveries among rejected null hypotheses. The significance of differences in correlations across hemispheres was examined at posterior sites where group differences in alpha asymmetry were present (P3,P4), as well as over frontal (F3,F4) and central (C3,C4) sites, using t-tests. We also assessed whether cortical thickness mediated the association of familial risk with EEG alpha power for eyes closed minus eyes open using standard procedures for mediator analyses [MacKinnon et al., 2007; Peterson et al., 2009].

RESULTS

We detected a significant hemispheric asymmetry of EEG alpha at parietal sites ($F = 7.14$, d$f = (1,66)$, $P < 0.01$), but not at frontal or central electrode sites (Hemisphere × Region interaction: $F = 5.45$, d$f = 1,66$, $P < 0.01$). Alpha asymmetry (i.e., right–left hemisphere alpha power) differences between the high- and low-risk groups were greatest over parietal sites in the eyes closed condition (Group × Hemisphere × Region × Condition interaction: $F = 4.47$, d$f = 1,66$, $P < 0.025$). Alpha asymmetry differed significantly between the high- and low-risk groups at parietal sites in the eyes closed but not eyes open condition, which was supported by a three-way interaction of Group ×
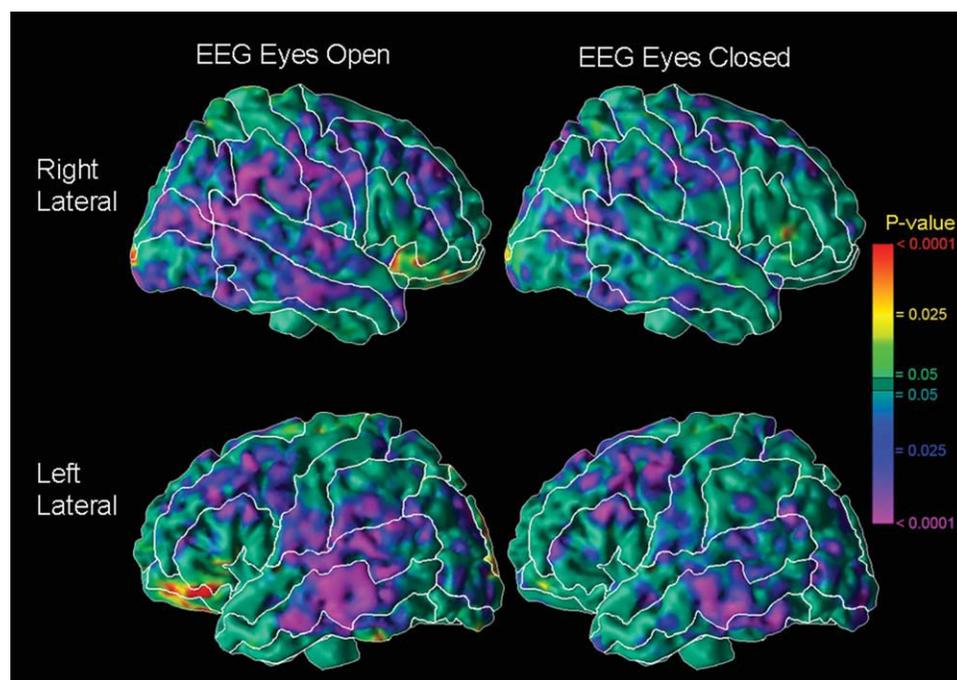
Figure 2.
Probability maps for correlations between EEG alpha power and MRI cortical thickness for eyes open and closed conditions mapped onto each hemisphere for both groups combined while covarying for age, sex, and risk group. Maps are corrected for multiple comparisons by controlling the false discovery rate.

Hemisphere × Condition interaction ($F = 4.87$, d$f = 1,66$, $P < 0.05$). The high-risk group showed greater alpha asymmetry, indicating relatively less cortical activity over right parietal sites, when compared to low-risk group in the eyes closed condition ($F = 4.32$, d$f = 1,66$, $P < 0.05$). When examining individual parietal sites, there was a significant condition-related difference in alpha asymmetry between high and low risk groups over medial parietal sites (P3,P4; $F = 5.31$, d$f = 1,66$, $P < 0.05$), but this difference only approached significance over lateral parietal sites (P7,P8; $F = 3.50$, d$f = 1,66$, $P = 0.07$). The difference in asymmetry between high- and low-risk groups was not likely due to an age difference for three reasons: (1) there was no interaction involving age and risk status in the above analysis; (2) alpha asymmetry at parietal sites did not significantly correlate with age ($r = -0.19$, ns), and age was included as a covariate in the analysis; and (3) maps showing EEG alpha and group differences included age as a covariate.

The left panel of Figure 1 shows the alpha power mapped onto a surface rendering of the template brain, representing surfaces of the right and left cerebral hemispheres that underlie EEG measures. The high-risk group showed relatively less cortical activity (greater alpha) over the right occipitoparietal region with eyes closed than open, whereas this was less evident in the low-risk group.

The significance of this group difference was confirmed by probability mapping (right panel of Fig. 1).

As indicated in Table I, the rate of lifetime major depression was higher in the high-risk than low-risk group ($\chi^2 = 13.89$, d$f = 1$, $P < 0.001$), as was the rate of lifetime anxiety disorders ($\chi^2 = 13.34$, d$f = 1$, $P < 0.001$). An analysis of covariance was therefore performed to determine whether the above difference in parietal alpha asymmetry between high- and low-risk groups remains after controlling for the presence of these disorders. This analysis used the factors in the above analyses with an age covariate, but including as an additional factor (Disorder)—whether the high- and low-risk participants had a major depressive or anxiety disorder. Thirty-seven subjects had either or both disorders (27 HR, 10 LR) and 38 had neither disorder (10 HR, 28 LR). This analysis yielded the same condition-related difference in parietal alpha asymmetry between the high- and low-risk groups as in the above analyses (Risk × Hemisphere × Condition interaction, $F = 4.35$, d$f = 1,66$, $P < 0.05$). The asymmetry difference between high- and low-risk groups did *not* depend on whether the participants had a major depressive or anxiety disorder, i.e., there was no higher order interaction involving Risk × Hemisphere × Condition × Disorder, $F = 0.92$, d$f = 1,66$, $P = 0.34$. There was also no significant main effect or other interaction involving the factor of Disorder.

Figure 2 shows probability maps for voxel-wise correlations of alpha power with MRI measures of cortical thickness for both groups combined, while covarying for age, gender, risk, and group. The maps demonstrate spatially extensive inverse correlations across the MRI and EEG measures, indicating that progressively thinner cortices were accompanied by progressively less cortical activity (greater alpha power). The same pattern of correlations was present for each risk group separately, with no significant interaction of risk group with EEG alpha power detectable in any regions. At medial parietal sites (P3,P4), where condition-related differences in alpha asymmetry between high and low risk groups were present, there was a significant difference in the correlation of MRI and alpha power over the right and left hemisphere in both eyes closed ($t = 3.06$, $P < 0.005$) and eyes open conditions ($t = 3.31$, $P = 0.001$). An inverse correlation between MRI and alpha was present at the right parietal site (P4), but not at the left parietal site (P3). There was, however, no significant hemispheric difference in the correlations at frontal (F3,F4) or central sites (C3,C4). Also, mediator analyses showed no evidence that cortical thickness mediated the relationship between risk status and alpha power (eyes closed-open) at posterior sites (all $P > 0.05$).

DISCUSSION

Offspring and grandchildren of probands having major depression, who are at particularly high risk for depressive disorders [Weissman et al., 2005], showed greater alpha asymmetry, with relatively less cortical activity over right parietal sites, compared to those at low risk. Their parietal asymmetry resembled that seen in adolescents and adults having a depressive disorder [Bruder et al., 1997; Davidson et al., 1987; Kentgen et al., 2000; Reid et al., 1998]. There was, however, no evidence in high risk offspring or grandchildren of the frontal alpha asymmetry seen in depressed individuals [Davidson et al., 1987; Gotlib et al., 1998; Henriques and Davidson, 1991]. The difference in parietal asymmetry between high- and low-risk groups did not depend on having a lifetime diagnosis of major depression or anxiety disorder, and prior findings also suggest that this alpha asymmetry is not state-dependent, but may represent a trait marker of vulnerability for depression. Relatively less right parietal activity was found in members of both second and third generations who did not have a depressive disorder but were at high risk [Bruder et al., 2005, 2007]. It was also present in remitted depressed adults who were euthymic during EEG testing [Henriques and Davidson, 1990]. Moreover, depressed patients who responded to an SSRI antidepressant showed this parietal asymmetry both before and after successful treatment, further suggesting that the finding is stable and state-independent [Bruder et al., 2008]. Studies indicate that about 60% of the variance of resting alpha asymmetry is attributable to a temporally stable latent trait [Hage-

mann et al., 2005]. Also, the findings for high risk subjects contrast with the decreased alpha seen for neurodegenerative disorders [Babiloni et al., 2008], indicating that they are not likely due to neuropathology, but rather to a trait associated with a familial form of depression.

Anatomical MRI findings [Peterson et al., 2009] for offspring and grandchildren at risk for depression led us to examine the relation of EEG alpha to cortical thickness in a subsample having both MRI and EEG measures. Although studies have reported that resting alpha power correlates inversely with cerebral metabolism or blood flow [Gonçalves et al., 2006; Sadato et al., 1998], ours is the first report of spatially extensive inverse correlations between alpha power and local measures of cortical thickness. Less cortical activity (greater alpha power) was associated with progressively greater cortical thinning particularly over the right posterior cortex, where significant differences in alpha were present between high and low risk groups. Correlations between alpha power and cortical thickness, as well as hemispheric differences in these correlations, were more evident over posterior than frontal sites. Although this might suggest that cortical thickness is more specific to understanding differences in posterior than frontal alpha, the correlations reflected a general relationship between alpha power and cortical thickness that was present across both high- and low-risk individuals. The spatially extensive inverse correlations of alpha power with cortical thickness raise the possibility that cortical thinning may in part account for the global enhancement of alpha reported in patients having a depressive disorder [Pollock and Schneider, 1990; Shagass et al., 1988] or in a putative subtype of patients who respond favorably to SSRI antidepressants [Bruder et al., 2008]. We detected no statistical evidence, however, to support the hypothesis that cortical thinning in right hemisphere regions mediated the relation between familial risk for depression and alpha asymmetry. Alpha asymmetry indicating relatively lower cortical activity over right posterior sites and cortical thinning may therefore be separate risk factors for depression. Although the spatial resolution of the EEG montage was suboptimal for a precise localization, the interpolated EEG alpha topographies (see Fig. 1) do show the expected maximum over posterior (visual) areas, which is consistent with its condition dependency, i.e., greater alpha in eyes closed condition. The condition-related differences between high- and low-risk groups in alpha power map widely over the posterior region of the template brain. Further study using high-resolution EEG methods (high-density montage and current source density measures) will more precisely detail the relationship between alpha and anatomical MRI.

A neuropsychological model hypothesizes that reduced right parietotemporal activity in depression generates low emotional arousal [Heller et al., 1995]. The right parietal cortex is known to subserve perception of emotion, and cortical activity over this region during emotional perception is reduced in depressed patients [Deldin et al., 2000;

Kayser et al., 2000], suggesting that reduced activity of the right parietal cortex in depression has important consequences for emotional processing. A magnetoencephalography study also found reduced cortical activity over the right temporoparietal region in depressed persons relative to controls during the viewing of emotionally arousing pictures, indicating that depressed individuals have difficulty activating cortices that subserve the arousal dimension of emotion [Moratti et al., 2008].

Although electrophysiological studies in high-risk samples are few, preliminary evidence suggests that children at risk for depression may show abnormal emotional reactivity and hemispheric asymmetries. Most notably, low positive emotionality in children, identified as conferring elevated risk for developing depression, was associated with an EEG alpha asymmetry indicating the presence of less right than left cortical activity, particularly over parietal sites [Shankman et al., 2005]. Given evidence for the importance of the right parietal cortices in processing emotional stimuli, high-risk children who have relatively low cortical activity of the right parietotemporal region may be less able to perceive, process, and respond to emotional information, placing them at increased risk for depression. MRI and neuropsychological findings support a model postulating that familial risk for depression produces cortical thinning of the right hemisphere, which in turn disrupts attention and arousal processes, and these disruptions increase the risk for developing a major depressive disorder [Peterson et al., 2009]. The extent to which EEG measures, alone or in combination with MRIs, might serve as a biological marker for predicting later onset of depressive disorders is currently under study.

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