Electroencephalographic Asymmetries in Adolescents With Major Depression: Influence of Comorbidity With Anxiety Disorders

Lisa M. Kentgen, Craig E. Tenke, Daniel S. Pine, Regan Fong, Rachel G. Klein, and Gerard E. Bruder
New York State Psychiatric Institute

This study examined whether adolescents with major depressive disorder (MDD) display the abnormal electroencephalographic (EEG) alpha asymmetries found in depressed adults. Resting EEG was recorded in 25 right-handed female outpatients (19 with MDD, 11 of whom also had a current anxiety disorder; 6 with anxiety disorders only) and 10 non-ill controls. In contrast to the non-ill controls, adolescents having MDD but no anxiety disorder showed alpha asymmetry indicative of less activation over right than over left posterior sites. Within the MDD patient group, comorbid anxiety disorders reduced the posterior alpha asymmetry, supporting the potential importance of evaluating anxiety in studies of regional brain activation in adolescent MDD. These preliminary findings are similar to those from adult studies that suggest that MDD is associated with right parietotemporal hypoactivation.

Functional brain asymmetry has been shown to play a role in mood regulation (Sackeim, 1991), and resting EEG patterns distinguish depressed from nondepressed adults. Abnormal regional brain asymmetries have been reported in clinical samples of adults with MDD and in nonclinical samples of adults who report depressive symptoms. Specifically, greater left than right frontal EEG alpha has been reported in currently or previously depressed adults (Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990, 1991), as well as in college students with elevated depression scale scores (Schaffer, Davidson, & Saran, 1983). Focus on the alpha band derives from evidence indicating an association between increased alpha activity and decreased cerebral activation (Shagass, 1972). Thus, greater alpha power over left than right frontal regions suggests greater right frontal activation in depression (e.g., Davidson, Ekman, Saran, Senulis, & Friesen, 1990; Tucker, Stenslie, Ross, & Shearer, 1981).

Some studies have found alpha asymmetry at posterior sites in adults with MDD, indicative of reduced right-sided relative to left-sided activation (Bruder et al., 1997; Henriques & Davidson, 1990; Reid, Duke, & Allen, 1998), and it has also been found in nonclinical groups scoring high on depression indices (Henriques

& Davidson, 1997). Two of these studies found abnormal alpha asymmetry in frontal and posterior regions (Bruder et al., 1997; Henriques & Davidson, 1990). Bruder et al. (1997) found this abnormal left-greater-than-right frontal asymmetry in depressed persons with comorbid anxiety disorders only. Their findings are consistent with a theory of an inverse relationship between anterior and posterior asymmetries, with lower-left frontal and right-posterior activation in depression.

Inconsistent alpha asymmetry findings in adult depression, particularly for posterior regions, have led to a search for mediating factors (e.g., see Reid et al., 1998). Heller and Nitschke (1998) have suggested that right-posterior activation associated with anxiety or anxious arousal could offset the effects of depression on alpha asymmetries. If so, failure to account for the presence of anxiety disorders, known to be highly comorbid with MDD, might account for inconsistent findings of reduced right-posterior activity. This possibility is supported by findings of right-greater-than-left alpha asymmetry in depressed patients both with and without an anxiety disorder (Bruder et al., 1997). Patients having MDD without an anxiety disorder showed evidence of less activation over right posterior sites than over left posterior sites, whereas those patients with an anxiety disorder had the opposite, left-greater-than-right alpha asymmetry.

Many cases of adult depression begin during childhood (Pine, Cohen, Gurley, Brook, & Ma, 1998). Studies of brain asymmetry profiles in childhood MDD may reveal biological correlates developed early in the course of a potentially chronic illness, as opposed to correlates that develop as the illness progresses into adulthood. Our study addresses the following hypotheses: (a) Depressed adolescents show relatively greater alpha power over left than right anterior sites, and (b) depressed adolescents show relatively greater alpha power over right than left posterior sites, but this posterior asymmetry is present mainly in depressed adolescents without comorbid anxiety.

We compared EEG alpha asymmetries across four groups: (a) adolescents with current MDD, but without a current anxiety disorder, (b) adolescents with current MDD and a current anxiety disorder, (c) adolescents with one or more current anxiety disor-

ders, but without comorbid MDD, and (d) adolescents with no lifetime history of psychiatric illness.

Method

Participants

EEG was recorded from adolescents, 25 right-handed female outpatients with MDD or anxiety disorders, and 10 non-ill controls. Girls were selected because (a) they are overrepresented among adolescents with MDD, and (b) gender may impact on multiple measures of hemispheric asymmetry (Bryden, 1982). The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM–IV;* American Psychiatric Association, 1994) criteria for mood or anxiety disorders were applied. Three patient groups were identified: (1) MDD only (*n* = 8), (2) MDD + anxiety (*n* = 11) and, (3) anxiety only (*n* = 6). The non-ill comparison group was recruited through advertising. Informed-consent and assent were obtained from guardians and participants. Participants were medication-free and medically healthy. Exclusion criteria were mental retardation, current psychosis, substance abuse, hearing impairment, and a history of bipolar disorder, head trauma or neurological disorder. Ages ranged from 12.2–18.8 years, mean age for all participants was 15.5 years. The groups did not differ by age or ethnicity.

For patients to enter the study, we required they meet full *DSM–IV* diagnostic criteria for current MDD or an anxiety disorder using clinical information obtained from the adolescent and parent. Anxiety disorders included generalized anxiety disorder, social phobia, separation anxiety disorder, and panic disorder. Diagnostic interviews were conducted with all children and English-speaking parents. The interview we used depended on the treatment study in which the child was enrolled. The same two clinicians evaluated all of the parents and children. Parents were evaluated using the Schedule for Affective Disorders for School Age Children lifetime version (K–SADS; Orvaschel, Puig-Antich, Chambers, Tabrizi, & Johnson, 1982) or the Parent as Respondent Informant Schedule (PARIS; Kentgen, Klein, Mannuzza, & Davies, 1997). We conducted direct interviews of adolescents with the PARIS or with the Diagnostic Interview Schedule for Children (DISC–2.3–C; Shaffer, Fisher, Dulcan, & Davies, 1996).

Patients entered the study only if both the standardized instrument and the clinical interview confirmed the diagnoses. Likewise, controls entered the study only if both the standardized instrument and the clinician confirmed the lifetime absence of all Axis I disorders. Final diagnostic decisions for current diagnoses were made using the best-estimate procedures (Leckman, Sholomaskas, Thompson, Belanger, & Weissman, 1982) with all information used.

Of the 11 MDD + anxiety adolescents, 3 had a single anxiety disorder and 8 had two or more anxiety disorders. The frequency of anxiety disorders in this group was 4 panic disorder, 7 social phobia, 2 separation anxiety disorder (SAD), 1 posttraumatic stress disorder (PTSD), and 4 generalized anxiety disorder. One patient in the comorbid group had oppositional defiant disorder (ODD), 2 had enuresis, and 1 had dysthymic disorder. Two patients in the anxiety only group had a single anxiety disorder, and 4 had two or more anxiety disorders. Of the 6 girls in the anxiety only group, 5 had panic disorder, 2 had social phobia, 2 had SAD, and 1 had PTSD. The only other comorbid diagnosis in the anxious only group was ODD (*n* = 1).

Procedure

We tested patients after a drug-free period of at least 2 weeks, although most patients were drug-free for longer or had never received psychotropic treatment. Resting EEG was recorded while participants sat in a sound-attenuated booth. EEG was recorded during two 3-min periods (eyes open and closed), during which participants were instructed to remain still and

to inhibit blinks or eye movements. During the eyes-open condition, participants fixated on a small cross centrally located on a computer screen.

Electrophysiological recording. Scalp EEG was recorded from two homologous pairs of electrodes overlying anterior (F3/F4, F7/F8), central (C3/C4, T7/T8), and posterior (P3/P4, P7/P8) brain regions over both left and right hemisphere, and also from two midline electrodes (Cz, Pz) using an electrode cap (Electro Cap International, Inc., Eaton, OH) with a nose reference.[1] Standard Beckman Ag/AgCl electrodes at right supra- and infra-orbital sites were used to monitor eyeblinks and vertical eye movements, and electrodes at right- and left-outer canthi were used to monitor horizontal eye movements. All electrode impedances were below 5 kΩ. EEG was recorded through a Grass Neurodata acquisition system (West Warwick, RI) at a gain of 10 k (5 k for eye channels), with a bandpass of 0.01–30 Hz.

A PC-based EEG acquisition system (Neuroscan Labs, Sterling, VA) acquired and digitized the data continuously at 100 samples/sec over each 3-min recording period. We chose this period on the basis of previous studies that have shown total recording periods as brief as 2 or 3 min are adequate to produce reliable estimates of alpha power in normal or depressed adults (Bruder et al., 1997; Henriques & Davidson, 1991).

Electrophysiological analyses. Data were segmented into consecutive 1.28-sec epochs every 0.64 sec (50% overlap). We excluded epochs contaminated by eye movements and movement-related artifacts using a rejection criterion of ±100 µV on any channel. These criteria produced artifact-free data as confirmed by direct visual inspection of the raw data. The EEG was tapered over the entire 1.28 sec by a Hanning window to suppress spectral side lobes (Bendat & Piersol, 1971). Data near the beginning and the end of each epoch, which had been attenuated by the Hanning window, were recovered in consecutive overlapping epochs.

Power spectra were computed off-line from EEG data using a Fast Fourier Transform. At each electrode site, alpha power was averaged for artifact-free epochs spanning each 3-min recording period for each participant and then integrated over 7.8–12.5 Hz. Logarithms of alpha power were computed to normalize the data.

Statistical analyses. To generate regional alpha values, electrode sites were pooled within anterior, central, and posterior regions for each hemisphere. To examine the hypothesized asymmetries, we computed log alpha power at each region for each hemisphere and compared them using repeated measures analysis of variance (ANOVA), with two between-subject-factors: Depression (MDD, no MDD) and Anxiety (anxiety, no anxiety). Within-subject factors were Hemisphere (left, right) and Region (anterior, central, posterior). We evaluated *F* ratios using degrees of freedom computed with the Greenhouse–Geisser epsilon correction, where appropriate, to counteract heterogeneity of variance–covariance matrices associated with repeated measures (Jennings & Wood, 1976). Effect sizes were evaluated from the partial eta squared (η^2) values produced by the ANOVA results. As described by Cohen (1988), $\eta^2 > .010$ = small effect size (*f* > .10); $\eta^2 > .059$ = medium effect size (*f* > .25); and $\eta^2 > .138$ = large effect size (*f* > .40). Significant interactions were further examined from simple effects as well as from independent ANOVAs of pairs of groups.

After the expected posterior topography of alpha and its enhancement in the eyes-closed condition were verified, we restricted examination of group differences to mean log-alpha power computed across conditions. This

[1] We used a nose reference to match the reference scheme used in a prior study of adults with MDD with or without an anxiety disorder (Bruder et al., 1997). This site is relatively inactive and its midline location should not distort EEG asymmetry measures. In the prior study, the use of a nose reference yielded significant differences in frontal alpha asymmetry among anxious MDD, nonanxious MDD, and control groups, whereas a Cz reference did not. Alpha asymmetries for posterior sites were, however, essentially the same for these two reference schemes.

method has been found to preserve the alpha asymmetries (e.g., Bruder et al., 1997).

Topographic maps. Topographic maps were generated to illustrate significant interactions in the ANOVA involving region and hemisphere. Log-alpha power at each electrode was projected onto a topographic map of the scalp, linearly interpolated between electrode sites, and coded into a 15-color scale.

Results

Regional alpha asymmetry was significantly associated with depression and anxiety (Region × Hemisphere × MDD × Anx-

iety, $F(2, 62) = 7.92; p < .002; \epsilon = .84, \eta^2 = .20346$). The interaction reflects a difference among the four groups in alpha asymmetry at posterior, but not at anterior sites (see Figure 1). Namely, the nonanxious MDD group showed significantly greater alpha (less activation) over right than left posterior sites, whereas anxious and control groups showed little or no asymmetry at these sites. There were no other significant effects involving the grouping factors of MDD or anxiety status.

Analyses of simple effects were used to further evaluate the four-way interaction. Examination of simple effects for each anxiety grouping (present and absent) revealed that differences in
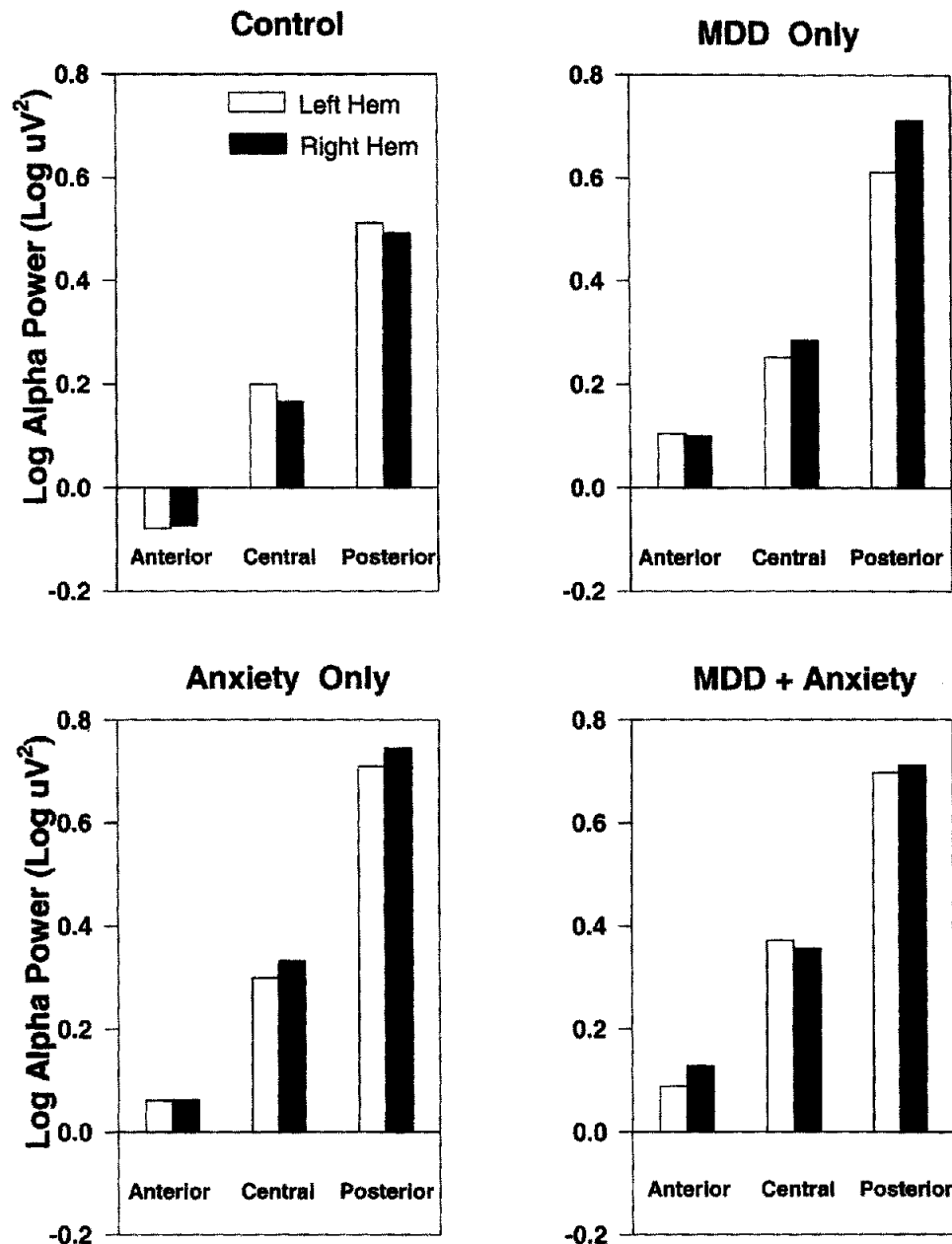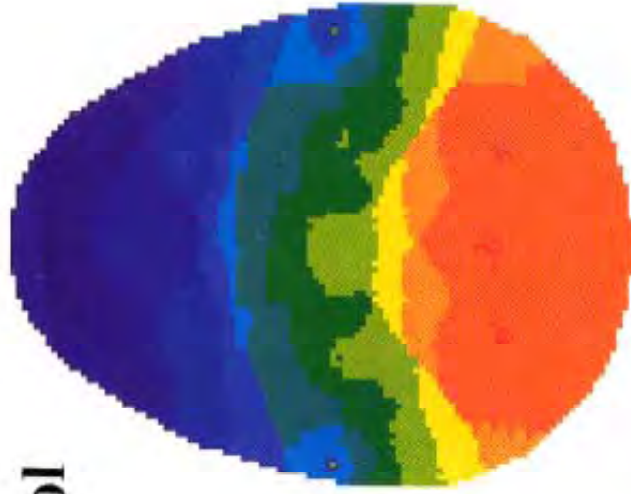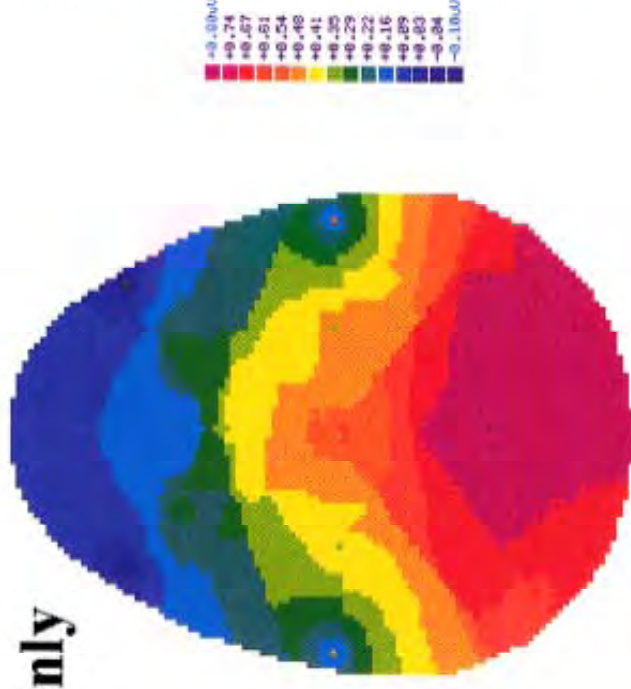

Figure 1. Regional alpha asymmetry was significantly associated with depression and anxiety. Interaction reflects a difference among the four groups in alpha asymmetry at posterior but not anterior sites. MDD = major depressive disorder; Hem = hemisphere.
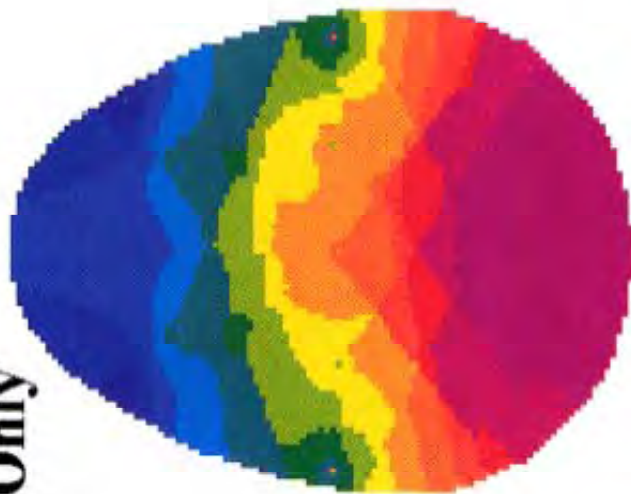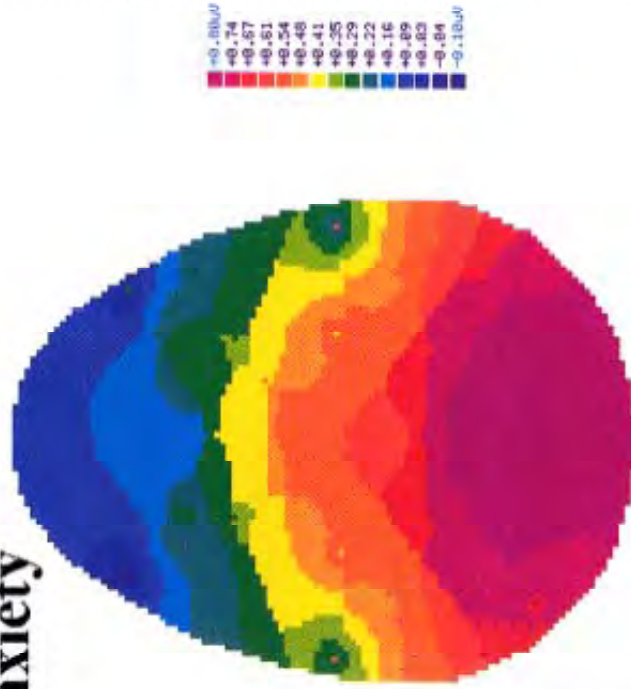
Figure 2. Maps of the topography of alpha power illustrate the posterior asymmetry for each group. MDD = major depressive disorder.

regional asymmetry between depressed and nondepressed participants were significant for the nonanxious groups (MDD × Region × Hemisphere, $F(2, 62) = 6.89, p = .004, \epsilon = .84$), but not for the anxious groups (MDD × Region × Hemisphere, $F(2, 62) = 2.76, p = .08, \epsilon = .84$). Among depressed patients, comorbid anxiety was associated with reduced alpha asymmetry. Simple effects analyses for each MDD grouping (present or absent) indicated a significant difference in regional asymmetry between depressed patients with and without comorbid anxiety (Anxiety × Region × Hemisphere, $F(2, 62) = 7.48, p = .002, \epsilon = .84$), but no difference in regional asymmetry between the nondepressed anxious and control groups.

Pairwise group comparisons yielded a significant difference in regional alpha asymmetry between the nonanxious MDD and non-ill controls (Group × Region × Hemisphere, $F(2, 32) = 5.87$, $p = .012, \epsilon = .80; \eta^2 = .26831$). Further analyses indicated that this finding was due to alpha asymmetry differences between nonanxious MDD and control groups at posterior sites: $F(1, 16) = 4.49, p = .050; \eta^2 = .21916$. The asymmetry was not clear at central sites $F(1, 16) = 2.90, p = .108, \eta^2 = .15343$, and was absent at anterior sites: $F(1, 16) = 0.11, p = .739, \eta^2 = .00710$. A similar difference in regional asymmetry was present between the nonanxious MDD and anxious MDD group (Group × Region × Hemisphere, $F(2, 34) = 7.28, p = .008, \epsilon = .66; \eta^2 = .29978$). This difference was also clearer at posterior sites, $F(1, 17) = 3.13, p = .095, \eta^2 = .15551$, than at anterior sites, $F(1, 17) = 2.61, p = .124, \eta^2 = .13320$, or central sites, $F(1, 17) = 2.15, p = .161, \eta^2 = .11236$. The asymmetry was also because of a difference in alpha asymmetry at the posterior sites, $F(1, 17) = 3.13, p = .095$, but not at the other sites. None of the remaining pairwise group comparisons were significant.

Maps representing the complete topography of alpha power for each group (Figure 2) illustrate these effects as (a) the posterior asymmetry characteristic of MDD, (b) the reduction of the asymmetry in patients with comorbid anxiety, (c) the absence of this posterior asymmetry in participants without MDD.

Discussion

This study is the first to document abnormal EEG alpha patterns in clinically depressed adolescent females. Our findings confirm the hypothesis that alpha asymmetry at posterior sites is associated with adolescent major depression, and this association is most evident for depressed adolescents without a comorbid anxiety disorder. The posterior findings are consistent with those reported in adults (Bruder et al., 1997; Henriques & Davidson, 1990; Reid et al., 1998). At both age ranges, major depressive disorder without anxiety appears characterized by an alpha asymmetry indicative of less activation (greater alpha) over right than left posterior regions, whereas this alpha asymmetry was not evident in adolescents with no psychiatric disorder.

The findings of reduced right posterior activation suggest that abnormal brain asymmetry profiles are found early in the course of depression. This suggests common biological correlates of mood disorders in females from adolescence through adulthood. Such data, when coupled with data in adults, implicate parietal regions in emotion across development. The findings may provide a means for characterizing subtypes in terms of course, symptoms, treatment, and family history.

Depressed adolescents in our sample did not show the abnormal frontal-alpha asymmetry obtained in depressed adults. As some frontal regions do not mature before late adolescence, this finding could reflect true differences between childhood and adult MDD. However, given the small sample size, further study is warranted. Moreover, because of small sample size and the heterogeneity in anxiety diagnoses, more research is needed on the degree to which the presence of an anxiety disorder influences the posterior-alpha asymmetry in adolescent depression.

This study is the first to document right-posterior abnormalities in adolescent clinical depression by EEG. We suggest future research that integrates electrophysiological measures with neuropsychological tasks shown to differentiate depressed children from a control group. Such studies, in combination with imaging studies that examine subcortical structures, will clarify our understanding of the behavioral, emotional, and neurological correlates to adolescent depression.

References

American Psychiatric Association. (1994). *Diagnostic and Statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Bendat, J. S., & Piersol, A. G. (1971). *Random data: Analyses and measurement procedures.* New York: Wiley.

Bruder, G. E., Fong, R., Tenke, C. E., Leite, P., Towey, J. P., Stewart, J. E., McGrath, P. J., & Quitkin, F. M. (1997). Regional brain asymmetries in major depression with or without an anxiety disorder: A quantitative electroencephalographic study. *Biological Psychiatry, 41,* 939–948.

Bryden, M. P. (1982). *Laterality: Functional asymmetry in the intact brain.* London: Academic Press.

Cohen, J. (1988). In *Statistical power analysis for the behavioral sciences* (2nd ed.) (pp. 273–288). Hilldale, NJ: Erlbaum.

Davidson, R. J., Ekman, P., Saron, C., Senulis, R., & Friesen, W. V. (1990). Approach–withdrawal and cerebral asymmetry: Emotional expression and brain physiology I. *Journal of Personality and Social Psychology, 58,* 330–341.

Gotlib, I. H., Ranganath, C., & Rosenfeld, P. (1998). Frontal EEG alpha asymmetry, depression, and cognitive functioning. *Cognition and Emotion, 12,* 449–478.

Heller, W., & Nitschke, J. (1998). The puzzle of regional brain activity in depression and anxiety: The importance of subtypes and comorbidity. *Cognition and Emotion, 12,* 421–447.

Henriques, J. B., & Davidson, R. J. (1990). Regional brain electrical asymmetries discriminate between previously depressed subjects and healthy controls. *Journal of Abnormal Psychology, 99,* 22–31.

Henriques, J. B., & Davidson, R. J. (1991). Left frontal hypoactivation in depression. *Journal of Abnormal Psychology, 100,* 535–545.

Henriques, J. B., & Davidson, R. J. (1997). Brain electrical asymmetries during cognitive task performance in depressed and nondepressed subjects. *Biological Psychiatry, 42,* 1039–1050.

Jennings, J. R., & Wood, C. C. (1976). The ϵ-adjustment for repeated-measures analyses of variance. *Psychophysiology, 13,* 277–278.

Kentgen, L. M., Klein, R. G., Mannuzza, S., & Davies, M. (1997). Test–retest reliability of maternal reports of lifetime mental disorders in their children. *Journal of Abnormal Child Psychology, 25,* 389–398.

Leckman, J. F., Sholomaskas, D., Thompson, W. E., Belanger, A., & Weissman, M. M. (1982). Best estimate of lifetime psychiatric diagnosis: A methodological study. *Archives of General Psychiatry, 39,* 879–883.

Orvaschel, H., Puig-Antich, J., Chambers, W., Tabrizi, M., & Johnson, R. (1982). Retrospective assessment of prepubertal major depression with the Kiddie–SADS–E. *Journal of the American Academy of Child and Adolescent Psychiatry, 21,* 392–397.

Pine, D. S., Cohen, E., Gurley, D., Brook, J., & Ma, Y. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry, 55*, 56–64.

Reid, S. A., Duke, L. M., & Allen, J. J. B. (1998). Resting frontal electroencephalographic asymmetry in depression: Inconsistencies suggest the need to identify mediating factors. *Psychophysiology, 35*, 389–404.

Sackeim, H. (1991). Emotion, disorders of mood, and hemispheric functional specialization. In B. Carroll & J. Barrett (Eds.) *Psychopathology and the brain* (pp. 209–242). New York: Raven Press.

Schaffer, C. E., Davidson, R. J., & Saron, C. (1983). Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects. *Biological Psychiatry, 18*, 753–762.

Shaffer, D., Fisher, P., Dulcan, M. K., & Davies, M. (1996). The NIMH Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3): Description, acceptability, prevalence rates, and performance in the MECA study. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 865–877.

Shagass, C. (1972). Electrical activity of the brain. In N. S. Greenfield & R. A. Sternbach (Eds.), *Handbook of psychophysiology* (pp. 263–328). New York: Holt, Rinehart & Winston.

Tucker, D. M., Stenslie, C. E., Roth, R. S., & Shearer, S. L. (1981). Right frontal activation and right hemisphere performance: Decrement during a depressed mood. *Archives of General Psychiatry, 38*, 169–174.